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Progressive renal failure

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Progressive chronic renal failure is a clinically significant, permanent and increasing loss of renal function, usually recognised by finding a persistently rising serum creatinine. Chronic renal failure does not always progress; it is possible to have a raised but stable serum creatinine for over 20 years. However when renal function is severely impaired (eg serum creatinine >400 μmol/l) progression is usual even if the primary disease appears inactive.

Progressive renal insufficiency: the scale of the problem

A growing number of new patients require renal replacement therapy each year in Britian. A prospective study in three British centres showed the prevalence of renal insufficiency, defined as a serum creatinine >150 μmol/l, of 2,058 per million population (pmp)[1]. There were approximately 600 pmp with chronic renal failure not requiring renal replacement therapy and an annual incidence of 78 new patients pmp with end stage renal failure (ESRF) needing dialysis. Worldwide acceptance rates on to renal replacement programmes (in developed countries) range from 65 pmp in the UK to 169 in the US[2]. There are important differences in the incidence of ESRF according to age, gender (slightly higher in males) and race. In Western countries, the incidence is lowest in children (10 pmp/year) and highest in the elderly (>400 pmp/year in those over 75 years of age). In the US, the incidence of ESRF in African and native Americans (424 pmp/year) is nearly four times higher than in Caucasians (114 pmp/year)[3]. Similar observations have been made in the UK where the incidence is raised in those of Asian as well as Afro-Caribbean descent[4,5].

Mechanisms of progression to ESRF

Progression of CRF is associated histologically with progressive glomerulosclerosis, tubulo-interstitial fibrosis and vascular/arteriolar sclerosis. Over the last decade our understanding of the mechanisms involved in these scarring processes has substantially advanced.

Glomerulosclerosis is a feature of progressive renal scarring regardless of the nature of the initial nephropathy (glomerular, tubular or hypertensive), suggesting that it is one of the final common pathways of renal scarring leading to ESRF. Numerous hypotheses have been proposed to explain it, of which the most popular is that of Hostetter *et al*[6]. They postulated that loss of a substantial proportion of renal function caused the remaining nephrons to adapt by increasing their perfusion and filtration. Although beneficial in the short term, this adaptive process slowly led to attrition and sclerosis of the remaining nephrons. The damage was originally attributed to hyperfiltration but emphasis is now placed on the accompanying glomerular hypertension; this causes proteinuria which is almost universally associated with progression of renal disease[7,8], probably through damage to podocytes, capillary walls and mesangial cells. Hostetter *et al* postulated that a high protein diet would enhance hyperfiltration and accelerate glomerulosclerosis and progression to ESRF, while a low protein diet would attenuate the adaptive changes and slow progression.

Another hypothesis is that lipids are nephrotoxic, with the hyperlipidaemia of CRF accelerating glomerulosclerosis[9]. The pathogenesis of glomerulosclerosis resembles that of atherosclerosis, with involvement of

platelets, monocytes and foam cells. Cells infiltrating scarred glomeruli may release mitogenic and fibrogenic mediators – growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), and chemokines such as monocyte chemoattractant peptide-1 (MCP-1) [7]. Of these, TGF-β is thought to be the most fibrogenic[7]. The glomeruli cannot clear deposits of collagen, so fibrosis progresses.

The pathogenesis of *tubulo-interstitial fibrosis* has also attracted renewed interest because the severity of tubulo-interstitial scarring is a better predictor of renal insufficiency than glomerulosclerosis[10]. Postulated pathogenetic mechanisms, based on animal experiments, include hyperfunction of the remaining tubules, nephrotoxicity of lipids, carbohydrates, iron and oxygen free radicals[11], and a nephrotoxic effect of proteinuria[12,13]. Any of these mechanisms may initiate a final common path – stimulating tubular cells to release chemotactic factors which attract mononuclear cells capable of initiating inflammation and scarring[14]. Tubular cells and interstitial fibroblasts respond to the mitogenic and fibrogenic mediators by producing excess collagen for which there are no effective breakdown mechanisms.

Vascular sclerosis is also a feature of scarred kidneys. The hypertension that accompanies many chronic nephropathies is one cause but there must be others since the severity is often out of proportion to the hypertension. Arteriolar sclerosis contributes to scarring through ischaemia of the remaining tubules and interstitium which receive their blood supply through the glomeruli. A vicious cycle of increasing scarring, hypertension and vascular sclerosis leads to ESRF[15].

The management of progressive renal failure: experimental approaches

In a wide range of animal models dietary protein restriction slows the progression of renal insufficiency and renal scarring[16], presumably by reducing glomerular hypertension[6]. Other dietary manipulations which have slowed progression of renal failure in some models include restriction of phosphate, saturated fat, salt, calories and sucrose, and a high water intake[16].

Table 1. Factors affecting progression

Age
Sex
Race
Blood pressure
Primary renal disease
Proteinuria
Level of renal function
ACE gene polymorphism

Numerous pharmacological agents have proved effective in experimental animals, usually rats[17]. Antihypertensive agents reduce proteinuria and preserve renal function. Some experiments have suggested that ACEI are more effective than other antihypertensives, possibly because they lower both systemic and intraglomerular hypertension[17]. Others have found that the protective effect of antihypertensives depends on their control of systemic blood pressure regardless of their mode of action[18]. Other pharmacological interventions have included the use of anti-platelet agents and anti-coagulants, reduction of circulating monocytes and inhibition of their release products such as cytokines, chemokines and growth factors[18]. The administration to rats of neutralising antibodies to cytokines such as IL-1 and TNF-α, chemokines such as MCP-1, or growth factors such as PDGF and TGF-β, have all proved effective in reducing the severity of renal injury and scarring[7]. Receptor antagonists to cytokines and growth factors have reduced proteinuria, preserved renal function and attenuated scarring in experimental animals with progressive glomerulonephritis[7].

The management of progressive renal failure: human disease

The first task is to make a specific diagnosis, starting with history, examination, urinalysis and microscopy and renal ultrasound. In a minority of patients a treatable condition such as urinary obstruction will be found. In the majority the only measures available are those which will slow progression by the mechanisms described in the previous section. Before testing any of these experimental therapies in man one must recall the variables that influence progression (Table 1). The rate of progression varies widely between primary diseases and is most likely to affect those with already severely reduced renal function. Children fare better than adults; women are less likely to develop renal failure than men; Caucasians are less likely to develop renal failure than Afro-Caribbeans or Asians, and for the same disease Afro-Caribbeans lose renal function faster than Caucasians, as do Asians with diabetes; hypertension and proteinuria, especially in the nephrotic range, accelerate renal failure. Recent data suggest that polymorphisms of the ACE gene also influence progression of renal failure; the genotype DD which has a deletion in both genes is associated

Table 2. Controlled trials of a low protein diet

First author	No. of patients	Measurement	Conclusion
Rosman 1984[21]	228	reciprocal creatinine	benefit
Ihle 1989[22]	64	GFR	benefit
Williams 1991[20]	60	creatinine clearance	no benefit
Locatelli 1991[23]	456	plasma creatinine	borderline
D'Amico 1994[24]	128	creatinine clearance	benefit

Key Points

PROGRESSIVE CHRONIC RENAL FAILURE CALLS FOR:

- **Search for a primary diagnosis → treatment if effective**
- **Non-specific measures that retard progression:**
  - **Tight control of blood pressure (target 125/75) for diabetic nephropathy and other diseases with proteinuria (value in other diseases uncertain)**
  - **Choice of an ACE inhibitor as antihypertensive with due precautions, especially in the elderly**
  - **Avoidance of high protein diet (low protein diet is of uncertain value and requires nutritional monitoring)**
  - **Careful follow-up**
  - **Transfer to renal clinic – early if primary diagnosis unknown**
    – before serum creatinine reaches 300 μmol/l

with increased activity of angiotensin converting enzyme and faster progression as judged by retrospective studies in IgA nephropathy[19].

It is therefore clear that each therapy must be tested in blinded prospective controlled trials of adequate size to allow for these confounding factors; very few published studies meet these criteria. So far there are no adequate studies on the effect of dietary lipids. A small study showed no benefit from 30 minutes daily exercise. There was no benefit from a low phosphate diet[20]. Only two therapies have been seriously investigated: low protein diet and treatment of hypertension.

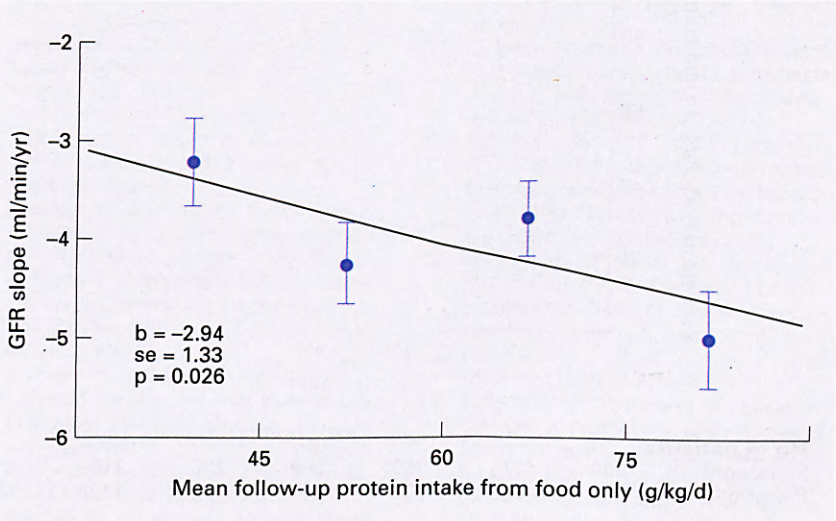
Low protein diet and tight control of blood pressure

In a meta-analysis of trials of low protein diet, only five controlled trials met the authors' criteria; they are listed in Table 2[21-24]. The overall impression was of a modest benefit from a difficult treatment to implement. As a controlled trial of treatment versus placebo in hypertensive patients with renal disease is unacceptable, the value of antihypertensives has been deduced from sequential studies which have been most convincing in diabetic nephropathy (see accompanying article by Dr Bilous). Alvestrand *et al*[25] found that the greater the fall in blood pressure on treatment, the greater the slowing in progression of renal failure after treatment.

The Modification of Diet in Renal Disease (MDRD) study performed in the US[26] included 585 patients with a GFR between 25 and 55 ml/min and 255 patients with values between 13 and 24 ml/min. Patients in both groups were randomly allocated a target mean blood pressure of 107 (standard control) or 92 mm Hg (tight control). In addition subjects in the first group were randomly allocated to a protein intake of 1.3 g/kg/day or 0.6 g/kg/day. The second group received 0.6 g/kg/day or 0.3 g/kg/day supplemented with a keto acid-amino acid mixture. Patients were followed for an average of 2.2 years. Projected mean decline in GFR at three years did not differ significantly between the diet groups and the BP groups, suggesting that neither protein restriction nor tight BP control was of value. However this view has been challenged on several scores.

Pendrini *et al*[27] carried out a meta-analysis on the first four studies in Table 2 and the MDRD trial. They concluded that the relative risk of renal failure was 0.67 (95% CI, 0.5-0.89) for a low protein diet. It should however be noted that the MDRD study found that the slope of plasma creatinine was altered by low protein diet independently of change in renal

Figure 1. Re-analysis of the MDRD study showing a significant increase in the rate of decline in GFR (-ve slope) with increasing protein intake. Redrawn from Levy *et al* 1996[29] with permission of the publisher.



function[28]. This makes it difficult to include the results of Rosman *et al*[21] and Locatelli *et al*[23] in any such analysis.

Recently Levy *et al*[29] have re-analysed the MDRD study to tease out the effect of compliance with diet and success in blood pressure control. They concluded that a 0.2 g/kg/day lower verified protein intake was associated with a 29% slower decline in GFR in patients whose initial value was less than 25 ml/min (Fig 1); the results were corrected for several variables such as primary disease, race and lipidaemia. This is a substantial gain but caveats are necessary. Statisticians look askance at post-hoc subgroup analysis. Patients in the MDRD did lose some weight; malnutrition is a risk factor for survival. The patient might gain more time before dialysis at the price of less time on dialysis.

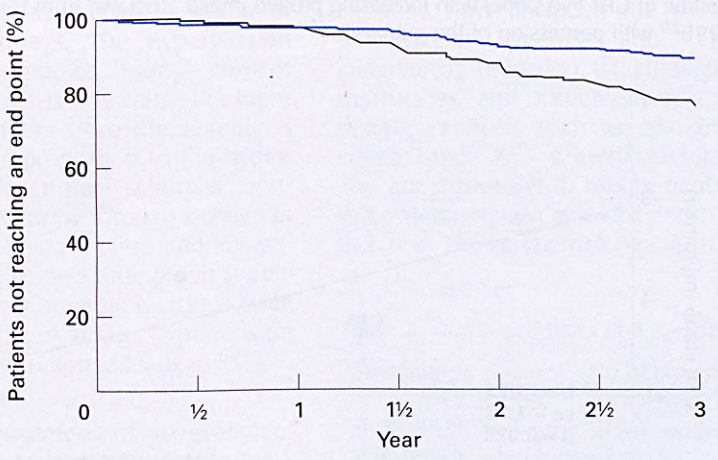
Blood pressure must be treated in its own right to reduce the risk of stroke, heart disease etc. A further analysis of the MDRD data shows that patients with proteinuria benefit from a lower blood pressure[30]. It is suggested that patients with proteinuria greater than 1 g/day should have a target blood pressure of less than 92 mmHg (125/75) and patients with values between 0.25 and 1 g/day should have a target less than 98 mmHg (130/80).

The next question is: 'which drug should be used to treat hypertension in chronic renal failure?' Results are conflicting. One study showed that enalapril was better than a beta blocker; another concluded that captopril was no better than nifedipine. A recent, large multicentre controlled trial concluded that patients receiving the ACEI benazepril had a 50% lower risk of doubling their serum creatinine as compared to placebo during a three year follow-up (Fig 2)[31]. As in the MDRD study, benefit was greatest for those with more than 1 g/day proteinuria; protein excretion fell significantly in the treatment group (Fig 3). Patients in both groups continued their previous (non-ACEI) therapy adjusted to reach the same target blood pressure, but in the event BP was lower in the treatment group, (Fig 3) so it is possible that some or all of the benefit was due to better BP control rather than any specific action of this class of drug. In a meta-analysis before this trial Gansevoort *et al*[32] concluded that ACEI reduced proteinuria more than other drugs. It remains to be seen whether this action will result in significantly better renal protection at the same level of blood pressure.

In summary

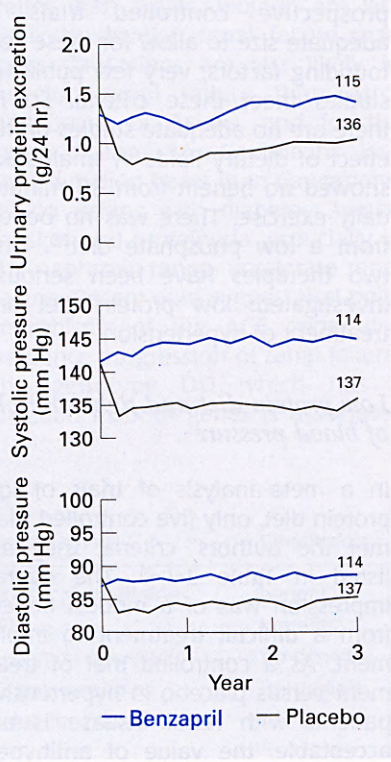
Blood pressure control is important and lower target values are required in those with proteinuria. ACEI are suitable agents provided the doctor is aware of the risks of renovascular disease in the elderly. Renal function should be checked after two weeks

Figure 2. Controlled trial of an ACE inhibitor (benazepril) and placebo in patients with BP controlled by other drugs; proportion of patients failing to reach an adverse end point (doubling of serum creatinine or need for dialysis) showing a significant advantage for benazepril ($p<0.001$). *Reprinted by permission of The New England Journal of Medicine* (31), *Copyright 1996, Massachusetts Medical Society.*



No of patients							
Benazepril	300	275	259	252	230	219	82
Placebo	283	252	236	217	198	179	53

Figure 3. Same study as Fig 2, showing reduction in proteinuria in the benazepril group and the unintended greater reduction in blood pressure in the benazepril group which complicates interpretation of the results. Numbers at right end of graphs are of patients completing the trial. *Reprinted by permission of The New England Journal of Medicine* (31), *Copyright 1996, Massachusetts Medical Society.*



treatment; deterioration calls for cessation of ACEI treatment and investigation for renal arterial disease.

Low protein diet should not be used routinely but high protein diet should be avoided. If a highly motivated patient wishes to try protein reduction in case it is beneficial, no less than 0.6g protein/day should be prescribed. The patient must be reviewed regularly by a specialist dietitian who can check nutritional state.

Regular medical follow-up is essential; it has been shown to slow progression of renal failure[33] probably because patients become more compliant with therapy, particularly antihypertensives. When should this follow-up be transferred to the renal unit? Studies from many countries have shown that late referral and/or emergency first dialysis are associated with substantially increased mortality and morbidity. Patients in whom the primary diagnosis is in doubt should be seen early; those in whom the cause is known, conservative treatment in place and without uraemic symptom should be transferred by the time the serum creatinine reaches 300 µmol/l.

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