vasculitis. Review. *J Am Soc Nephrol* 1997; **8**:314–22.
8 Lanham JG, Elkon KB, Pusey CB, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Review. *Medicine (Baltimore)* 1984;**63**:65–81.
9 Sinico RA, Ribero ML, Fornasieri A, Renoldi P, *et al*. Hepatitis C virus genotype in patients with essential mixed cryoglobulinaemia. *QJM* 1995;**88**:805–10.
10 Hall S, Barr W, Lie JT, Stanson AW, *et al*. Takayasu arteritis. A study of 32 North American patients. *Medicine (Baltimore)* 1985;**64**:89–99.
11 Bianco N, Vargas-Arenas R, Tapanes F, *et al*. Silent nephritis in systemic lupus erythematosus (SLE). *Scand J Immunol* 2001; **54**(Suppl 1):100.
12 Moroni G, Trendelenburg M, Del Papa N, Quaglini S, *et al*. Anti-C1q antibodies may help in diagnosing a renal flare in lupus nephritis. *Am J Kidney Dis* 2001;**37**:490–8.
13 Steen VD, Costantino JP, Shapiro AP, Medsger TA. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990;**113**:352–7.
14 Harper L, Cockwell P, Howie AJ, Michael J, *et al*. Focal segmental necrotizing glomerulonephritis in rheumatoid arthritis. *QJM* 1997;**90**:125–32.
15 Peat DS, Mathieson PW. Cholesterol emboli may mimic systemic vasculitis. *Br Med J* 1996;**313**:546–7.

Cardiovascular risk factors in progressive renal disease

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Cardiovascular disease (CVD) is one of the leading causes of mortality and morbidity in the western world. Epidemiological studies have identified important physiological and lifestyle risk factors for CVD (Table 1)[1]. More encouragingly, evidence from a number of randomised controlled trials and meta-analyses has now demonstrated that this disease may largely be prevented (at least in the general population) by lifestyle modification and drug treatment of risk factors[2]. However, cardiovascular risk management remains suboptimal, particularly in populations with certain chronic metabolic disorders such as chronic renal failure (CRF).

Chronic renal failure and cardiovascular disease

With modern nephrological management, the survival of patients with CRF has been greatly improved. Patients now survive their renal disease only to die prematurely of the complications of atherosclerosis, the most frequent cause of death in patients with end-stage renal disease[3]. Cardiovascular morbidity and mortality are both several-fold higher in patients with CRF than among the general population: for example, cardiac mortality in the USA for dialysis patients younger than 45 years is over 100 times that in the general population. Many – but not all – studies have demonstrated that even mild renal insufficiency is an independent risk factor for CVD[4,5]. Unfortunately, to date there have been no large-scale studies demonstrating that intervention can reduce the high cardiovascular risk in renal patients. However, it seems likely that cardiovascular risk factors present the same health hazards to patients with CRF as they do to the general population, and therefore that intervention to modify the risks will be beneficial.

Several mechanisms may explain the association between renal disease and CVD. Atherosclerosis will affect the main renal arteries in parallel with arteries elsewhere in the body, limiting blood flow and resulting in ischaemic damage. It is plausible that the same risk factors may promote intrarenal vascular disease, directly damaging glomeruli and tubules. It has also become apparent that glomerulosclerosis and atherosclerosis share a common pathophysiological aetiology[6]. Both processes are known to result from endothelial injury, macrophage infiltration, hyperlipoproteinaemia and

Key Points

- **Cardiovascular disease is common in patients with chronic renal failure (CRF)**
- **Atherosclerosis and glomerulosclerosis share a common aetiology and have common risk factors**
- **Therapies which slow the progression of CRF are likely to improve cardiovascular outcome, and *vice versa***
- **Antihypertensive medication (including angiotensin-converting enzyme inhibitors and lipid lowering agents) and smoking cessation should be part of a comprehensive therapeutic approach to the patient with CRF**

KEY WORDS: CPD, atherosclerosis, cardiovascular disease, chronic renal failure, dyslipidaemia, glomerulosclerosis, hypertension, smoking

Table 1. Modifiable risk factors for cardiovascular disease and progressive renal failure (indicating the level of supporting evidence for the risk factor in each setting).

Risk factor	Cardiovascular disease	Progressive renal failure
Hypertension	Strong epidemiological evidence Intervention studies show benefit in humans Added benefit from ACE inhibitors	Strong epidemiological evidence Intervention studies show benefit in humans Added benefit from ACE inhibitors
Hyperlipidaemia	Strong epidemiological evidence Intervention studies show benefit in humans	Some epidemiological evidence No intervention studies in humans Supportive intervention studies in animals
Smoking	Strong epidemiological evidence Intervention studies show benefit in humans	Some epidemiological evidence No intervention studies
Lack of exercise	Strong epidemiological evidence	Supportive intervention studies in animals
Obesity	Strong epidemiological evidence	No evidence
Inflammatory markers	Some epidemiological evidence	No evidence, but plausible hypothesis
Excess homocysteine	Some epidemiological evidence	Some epidemiological evidence
Anaemia	Some epidemiological evidence Intervention studies show potential benefit in humans	No evidence

ACE = angiotensin-converting enzyme.

hypertension (Fig 1). It is therefore not surprising that many of the factors known to accelerate atherosclerosis have also been implicated in the aetiology of CRF. In addition, it is probable that the uraemic environment is directly injurious to the cardiovascular system.

Risk factor modification

Progression of CRF can be inexorable once a critical reduction in renal mass has occurred[7]. There are currently few effective treatments for specific renal diseases, so nephrologists have concentrated on developing therapies aimed at modifying the common pathway leading to glomerulosclerosis[8]. Fortuitously, because of the shared aetiological factors, it is now apparent that therapies aimed at slowing progression of CRF may also retard the development of CVD, and *vice versa* (Table 1).

Hypertension

Effective treatment of hypertension slows the rate of progression of CRF[8], just as it has been conclusively shown to reduce cardiovascular death rates. Of note, angiotensin-converting enzyme (ACE) inhibitors convey benefit over and above that achieved by blood pressure lowering alone in both diabetic and non-diabetic renal disease[9,10]. This additional benefit may result from the unique action of ACE inhibitors on glomerular haemodynamics such that they cause a greater reduction in glomerular hypertension than might be expected by their systemic antihypertensive action. Non-haemodynamic benefits of ACE inhibitors, for example limiting cell proliferation and macrophage activation, and reducing the production of pro-fibrotic cytokines and extracellular matrix, may also contribute to their beneficial effect on CRF progression.

These benefits echo the substantial benefits reported with these agents on the evolution of CVD[11] and provide a rationale for the use of ACE inhibitors as the single most important intervention in patients with CRF. Whether angiotensin II receptor antagonists will be equally beneficial awaits further study, although early studies with this class of agents have been encouraging[12].

Dyslipidaemia

Dyslipidaemia due to disturbances in plasma lipoprotein metabolism is frequently detected in patients with CRF. It develops during the asymptomatic stages of renal insufficiency, becoming more pronounced as renal failure advances[13]. Data from epidemiological and observational clinical studies have now established beyond doubt a causal association between hyperlipidaemia and the development of CVD in the general population.

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduces the risk of myocardial infarction and cardiovascular mortality in hypercholesterolaemic patients[2]. It is highly likely that lipoprotein abnormalities contribute to the accelerated atherosclerotic process, and consequently to the high prevalence of CVD observed in individuals with CRF. Although it is now clear that HMG-CoA reductase inhibitors can effectively and safely improve lipid profiles in this group of patients, to date most of the major outcome trials have deliberately excluded patients with renal disease. Thus, the beneficial effects of therapy on CVD in renal patients must remain speculative until the results of ongoing studies in this group of patients are reported.

For almost 100 years it has been suggested that hyperlipidaemia might contribute to the progression of renal injury. More recently, several plausible mechanisms have been put forward[7]. Support for this hypothesis has been provided mainly by a number of experimental studies using animal models of renal disease. In these models,

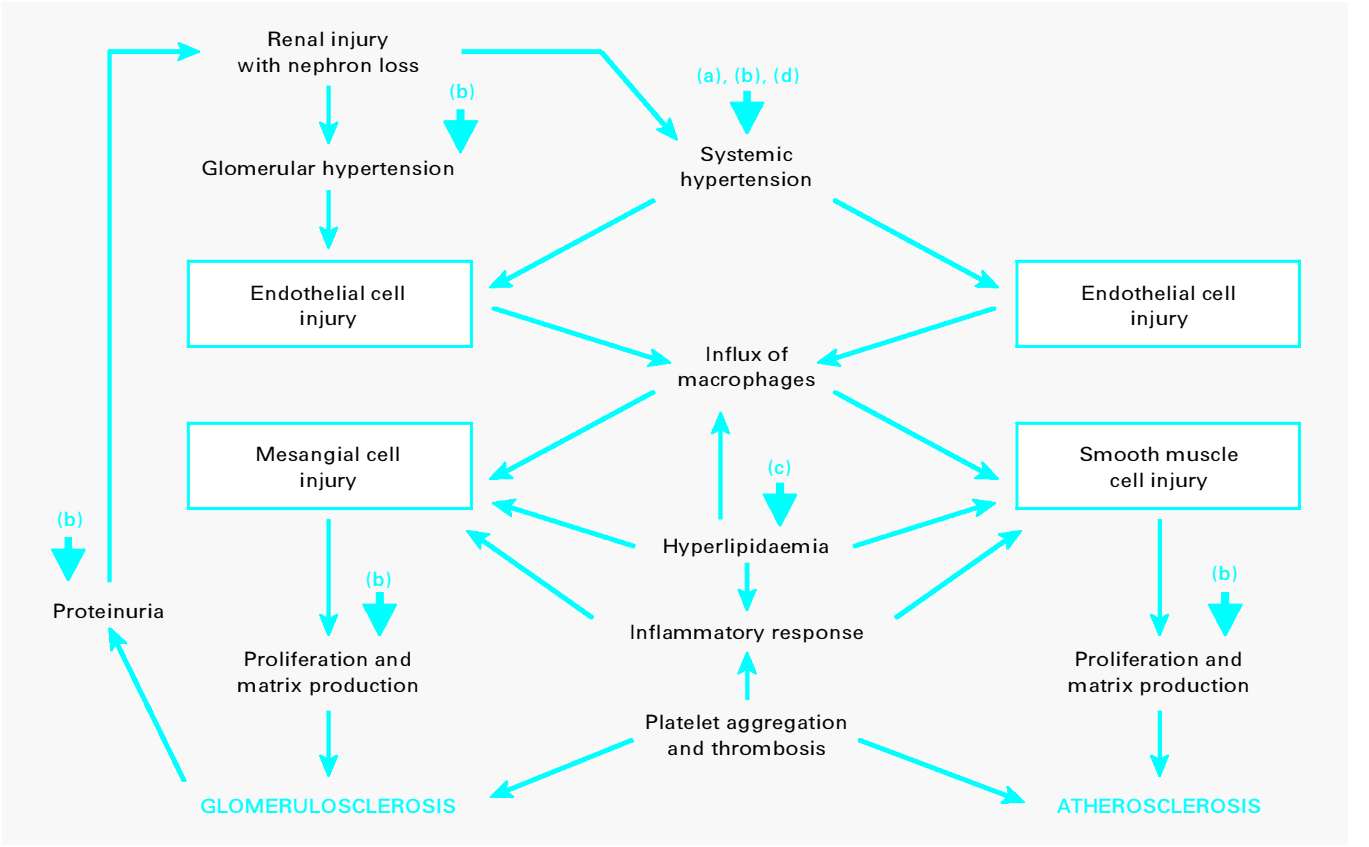

Fig 1. Diagram of possible common pathogenetic mechanisms in the development of glomerulosclerosis and atherosclerosis (bold arrow = potential target for therapeutic intervention likely to be effective in both disease processes: **(a)** antihypertensive medication, **(b)** angiotensin-converting enzyme inhibitors, **(c)** lipid lowering agents, **(d)** smoking cessation.

diet-induced hypercholesterolaemia worsens renal injury, while it is ameliorated by cholesterol lowering medications.

The evidence from human disease that treatment of hyperlipidaemia reduces progression of CRF is less conclusive. Epidemiological data suggest a role for hyperlipidaemia in the progression of diabetic nephropathy. Several small controlled trials have recently reported the effects of cholesterol reduction on progression in humans, but they were of insufficient power to demonstrate any benefit. A recent meta-analysis has shown that pharmacological lipid reduction may preserve glomerular filtration rate and decrease proteinuria in patients with renal disease. This study also suggested that lipid lowering agents might provide a benefit on progression of renal failure comparable with that observed with ACE inhibitors[14].

The exact mechanism by which lipid lowering may protect against the development of glomerulosclerosis is not known, but mesangial cells and vascular smooth muscle cells share common properties. Analogous to its role in atherosclerosis, low-density lipoprotein promotes mesangial cell proliferation and stimulates fibronectin and chemoattractant production. In glomerulosclerosis, this response would promote setting up a vicious circle in which the worsening renal disease then worsens the hyperlipidaemia. Reduction of lipid levels may also result in beneficial haemodynamic changes, with lowering of peripheral vascular resistance, increase in cardiac output and improvement of endothelial function. It remains unclear whether such effects are specific to the action of HMG-CoA reductase inhibitors, with which the majority of studies have been performed, or are due to the cholesterol lowering *per se*.

Smoking

The adverse cardiovascular health effects of smoking are widely known, but the addictive property of nicotine in tobacco smoke has resulted in an almost complete lack of change in the prevalence of smoking in recent years. More recently, it has been argued that the kidney is also an important target organ of smoking-induced damage, although not all studies support this theory. Smoking has been identified as a risk factor for the development of microalbuminuria in both Type 1 and Type 2 diabetes. In addition, the risk of progression in polycystic kidney disease and immunoglobulin A nephropathy appears to be increased up to 10-fold in smokers[15]. There are no prospective studies showing benefit from cessation of smoking, and nephrologists have largely neglected this issue. However, patients with progressive renal failure should be advised to stop smoking

for the beneficial effects on CVD, if not on progression.

The mechanisms by which smoking exerts its adverse effects on renal function have not been clarified, but mechanisms related to actions on both systemic blood pressure and renal haemodynamics have been suggested. Smoking may also indirectly damage the microvasculature (including the glomerulus) in the kidney through its known effects on platelet function, thromboxane metabolism and endothelial cell function[16].

Other risk factors

Patients with renal disease have a higher prevalence of less established cardiovascular risk factors, including low high-density lipoprotein cholesterol, and high triglycerides, lipoprotein (a) and homocysteine. They also exercise less than the general population. It remains unknown whether modifying these factors could impact on either CVD or progression of CRF.

Inflammatory cytokines have recently been implicated in the development of atherosclerosis, and similar mechanisms may also promote glomerulosclerosis. Inflammatory molecules are generally upregulated in CRF, but the relevance of this to human disease is speculative. It is possible that anti-inflammatory therapies might lessen atherosclerosis and slow the progression of CRF.

Patients with progressive CRF may have additional cardiovascular risk factors which are not usually found in the general population. One example is anaemia; its correction with recombinant human erythropoietin may ameliorate the development of cardiovascular morbidity and mortality in the long term, although the effect of correcting anaemia on progression of CRF is currently unknown.

Conclusions

The treatment goals in CRF should be renoprotection and limitation of CVD. These treatments are largely complementary and primarily include control of hypertension (with ACE inhibitors), lipid lowering therapy and cessation of smoking.

References

1 Sharp I (ed). *Looking to the future: making coronary heart disease an epidemic of the past*. London: The Stationery Office, 1999.

2 Wood D, Durrington P, Poulter N, McInnes G, *et al*. Joint British recommendations on prevention of coronary disease in clinical practice. *Heart* 1998;**80**(Suppl 2): S1–29.

3 Mallick NP, Jones E, Selwood N. The European (European Dialysis and Transplantation Association-European Renal Association) Registry. *Am J Kidney Dis* 1995;**25**:176–87.

4 Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Review. *Lancet* 2000;**356**: 147–52.

5 Kasiske BL. The kidney in cardiovascular disease. *Ann Intern Med* 2001;**134**:707–9.

6 Diamond JR, Karnovsky MJ. Focal and segmental glomerulosclerosis: analogies to atherosclerosis. Review. *Kidney Int* 1988;**33**: 917–24.

7 Klahr S, Schreiner G, Ichikawa I. The progression of renal disease. Review. *N Engl J Med* 1988;**318**:1657–66.

8 Taal MW, Brenner BM. Evolving strategies for renoprotection: non-diabetic chronic renal disease. Review. *Curr Opin Nephrol Hypertens* 2001;**10**:523–31.

9 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**:1456–62.

10 Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici Nefrologia). *Lancet* 1997;**349**:1857–63.

11 Yusuf S, Sleight P, Pogue J, Bosch J, *et al*. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**: 145–53.

12 Brenner BM, Cooper ME, de Zeeuw D, Keane WF, *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9.

13 Attman PO, Samuelsson O, Alaupovic P. Lipoprotein metabolism and renal failure. Review. *Am J Kidney Dis* 1993;**21**:573–92.

14 Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001;**59**: 260–9.

15 Orth SR, Stockmann A, Conradt, C, Ritz E, *et al*. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int* 1998;**54**:926–31.

16 Orth SR, Ritz E, Schrier RW. The renal risks of smoking. Review. *Kidney Int* 1997;**51**: 1669–77.