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How does early chronic kidney disease progress?

A Background Paper prepared for the UK Consensus Conference on Early Chronic Kidney Disease

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Introduction

Chronic Kidney Disease (CKD) may arise due to a multitude of different insults to renal function. However despite the wide range of pathological processes that may induce renal injury, substantial loss of nephrons provokes a common syndrome characterized clinically by systemic hypertension, proteinuria and a progressive decline in glomerular filtration rate (GFR) and patho-physiologically by progressive interstitial fibrosis, peritubular capillary loss with hypoxia and destruction of functioning nephrons because of tubular atrophy [1]. Extensive studies suggest that the rate of loss of GFR, that is the rate of progression of CKD, may be largely due to common secondary factors, often unrelated to the initial disease [2].

Some of these factors such as age and race are not open to intervention. The majority, however, provide at least a potential for intervention in order to slow or halt the progression of early CKD.

Factors influencing the progression of CKD

Intra-glomerular haemodynamic factors

In rat models, subtotal nephrectomy (remnant kidney model) leads to a compensatory hyperfiltration of the remaining nephrons initially maintaining overall GFR; however, over time glomerular hypertension, proteinuria and progressive CKD develop [3].

The loss of sufficient renal functional units (nephrons) from whatever insult, puts into place haemodynamic factors that perpetuate renal dysfunction. Indirect studies in humans strongly indicate a very similar response to those that are demonstrated in many animal models of progressive CKD, with increased intraglomerular pressure, glomerular hypertrophy and compensatory glomerular hyperfiltration.

The compensatory response to nephron loss of hyperfiltration in the spared nephrons, in an attempt to maintain GFR, leads to glomerular injury and the finding on renal biopsy examination of secondary glomerulosclerosis. Glomerular cell proliferation, macrophage infiltration and the progressive accumulation of extracellular matrix (ECM) components all may contribute to the development of the glomerular sclerotic lesion, stretching of the capillary tuft also stretches the adjacent mesangial cells and this induces mesangial proliferation. How these changes occur is not well understood, but cytokines such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) may be responsible for at least part of the matrix accumulation [4–6].

A surgical study shows the risk of developing secondary glomerulosclerosis after nephron loss to be proportional to the degree of initial loss and to require loss of at least 50% of functional renal tissue [7].

Early diabetic nephropathy is well described to be associated with hyperfiltration resulting in an elevation of GFR with associated glomerular hypertrophy [8,9]. Primary renal vasodilatation, with a greater reduction in afferent relative to efferent arteriolar resistance results in increased intraglomerular pressure and glomerular hyperfiltration.

There is correlation between urine albumin excretion and glomerular pressure, and therefore, as with the remnant kidney model, the glomerular hypertension in diabetic nephropathy propagates a decline in GFR at least partly due to increased protein leakage across glomerular capillaries into Bowman's space [10]. Segmental areas of glomerulosclerosis can also be induced by intraglomerular hypertension resulting from primary renal vasodilatation as it occurs in diabetic nephropathy [5].

The mechanisms underlying this afferent arteriolar dilatation in diabetics are not well understood: several factors may contribute. Hormonal influences may play

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a role: an infusion of the somatostatin analogue octreotide over 12 weeks was seen to partially reverse hyperfiltration and renal hypertrophy in type I diabetics, insulin-like growth factor (IGF-1) levels fell over the duration of the treatment [11]. Additionally, the infusion of IGF-1 in normal subjects induces vasodilatation, an elevation in GFR and increased urinary albumin excretion [12]. Atrial natriuretic peptide has also been postulated to play a role in hyperfiltration with its secretion being triggered by increased sodium reabsorption in the proximal tubule. Alterations in levels of endothelial-derived relaxing factor, angiotensin II, prostaglandins, thromboxanes and kinins have all been implicated in glomerular hypertension [13]. Other factors directly related to hyperglycaemia such as the intracellular accumulation of sorbitol and of initially reversible, and then irreversible glycosylation products may also play a role. Finally, enhanced proximal tubular sodium reabsorption due to sodium-glucose co-transport which is enhanced by hyperglycaemia, results in reduced distal sodium and fluid delivery resulting in activation of the tubuloglomerular feedback mechanism in the macula densa, raising the GFR via dilatation of the afferent arteriole [14].

Hyperfiltration has not been so well studied in non-diabetic renal disease but has been described in sickle cell anaemia, lupus nephritis, obesity and in white hypertensives with reduced numbers of hypertrophied glomeruli suggesting compensatory hyperfiltration [15].

Intraglomerular pressure may be raised in glomerular diseases as a compensatory adaptation to a reduction in the permeability of the glomerular capillary wall to small solutes and water. The fall in GFR is minimized by raising the intraglomerular pressure, a response that may be mediated by reduced flow to the macula densa and subsequent activation of tubuloglomerular feedback.

Intraglomerular hypertension and hypertrophy may further cause damage and progression of CKD as the increased wall stress and increased glomerular diameter cause detachment of the glomerular epithelial cells from the glomerular capillary wall. These areas allow increased flux of water and solutes; however, very large circulating macromolecules (such as IgM and fibrinogen and complement metabolites) cannot cross the glomerular basement membrane and are trapped in the subendothelial space. The characteristic accumulation of these 'hyaline' deposits can progressively narrow the capillary lumens, thereby decreasing glomerular perfusion and filtration [16].

Tubulo-interstitial disease

Impairment of kidney function correlates better with the degree of tubulo-interstitial injury and fibrosis than with histologically evident glomerular injury. Interstitial fibrosis results from increased synthesis and decreased breakdown of ECM [17].

In CKD, the balance between cell proliferation and apoptosis is disordered with excessive apoptosis of normal glomerular and tubular epithelial cells. Abnormally abundant apoptotic stimuli such as TGF-β, tumour necrosis factor (TNF), Fas ligand (FasL) and interferon-α result in increased cell death [18,19]. Tissue hypoxia from decreased perfusion of the microvasculature also stimulates FasL-mediated apoptosis. Hypoxia may be a cause as well as an effect of the progression of CKD; intertubular capillaries are reduced in CKD of all causes, an effect exacerbated by glomerular sclerosis. Increased interstitium also diminishes capillary perfusion of the tubules.

An excess of cytokines in the kidney in CKD recruits macrophages into the kidney; macrophage-colony stimulating factor is over expressed by the tubules as a response to injury. Macrophage infiltration of the interstitium correlates with renal dysfunction and the cells amplify the response by producing more cytokines further inducing fibrosis and apoptosis.

Clinically evident factors predicting accelerated progression of CKD

Hypertension [20–22] and proteinuria [22–24] are consistently demonstrated to be independent risk factors for the progression of CKD.

Systemic hypertension is common in CKD and incidence increases with declining GFR [25]. Hypertension is due to a combination of sodium and water excess, activation of the renin–angiotensin–aldosterone system and sympathetic nervous system activation. Systemic hypertension is transmitted causing glomerular capillary hypertension and a subsequent accelerated decline in GFR as outlined above (intra-glomerular haemodynamic factors).

The kidneys also generate angiotensin II locally, independent of the systemic system, and acting via the angiotensin II type 1 receptor this has significant non-haemodynamic effects contributing to the development of tubulo-interstitial fibrosis by stimulating expression of cytokines and growth factors favouring fibrosis and recruitment of macrophages [26]. Thus, the use of angiotensin-converting enzyme (ACE) inhibitors performs a dual role, both lowering the glomerular capillary pressure and preventing the increase in pro-fibrotic cytokine expression.

Proteinuria occurs as a result of glomerular capillary hypertension and varies directly with the intraglomerular pressure. The resulting damage to the permeability barrier in the glomerulus, a mechanism at least in part mediated by angiotensin II, leads to an excess of proteins reaching the lumen of the proximal tubules. Filtered proteins are taken up by the tubular cells by endocytosis and stimulate the abnormal production of cytokines which are released into the interstitium leading to macrophage and T lymphocyte migration, the proliferation of fibroblasts and increased ECM production: the familiar mechanisms of glomerulosclerosis and interstitial fibrosis [27]. Some specific

proteins may play an enhanced role: transferrin is seen to accumulate in the proximal tubular cells in proteinuric patients with CKD [28] and has been implicated in toxicity via lipid peroxidation and complement activation.

Consistent with this role in pathophysiology, proteinuria is a strong predictor of clinical progression of CKD, the rapidity of progression is proportional to the severity of proteinuria [29]. ACE inhibitors reduce proteinuria and limit the progression of deterioration of CKD both by reducing glomerular capillary hypertension and by reducing the mean dimensions of large unselective pores of the glomerular capillary wall so enhancing the size-selective function of this barrier to macromolecules.

Hyperlipidaemia is common in patients with CKD, particularly those with heavy proteinuria. In addition to the adverse effects upon systemic atherosclerosis, there is some evidence that hyperlipidaemia may also have an adverse impact upon progression of CKD [30,31]. Hyperlipidaemia activates mesangial cells, leading to mesangial proliferation, production of macrophage chemotactic factors, stimulation of reactive oxygen species and stimulation of growth factor and cytokine release. All of these factors may then contribute to renal injury and progression of CKD.

Phosphate retention occurs as soon as GFR begins to decline and the accumulation of phosphate contributes to progression of CKD. Phosphate precipitates with calcium in the interstitium initiating an inflammatory response resulting in interstitial fibrosis and tubular atrophy [32,33].

Anaemia occurs in CKD largely as a result of erythropoietin deficiency. In addition to increasing red cell mass and so tissue oxygen delivery, treatment with erythropoietin appears to have additional benefits of protecting against oxidative stress and tubular cell apoptosis and possibly stimulating angiogenesis. There is some clinical evidence that correcting anaemia slows the progression of CKD [34].

Experimental models suggest that the metabolic acidosis of CKD may also play a role in the progression of disease. As nephron numbers decline each nephron excretes more acid, mainly as ammonium. Hyperammoniagenesis may also result from intratubular catabolism of the excessive protein load associated with proteinuria. The local accumulation of ammonia can directly activate complement leading to secondary tubulointerstitial damage [35,36]. Buffering the acidosis with alkali therapy prevents the increase in ammonium production, and therefore should minimize renal injury. Whilst the renal protective effects of alkali therapy are unproven in clinical practice the prevention of osteopenia and muscle wasting still make such treatment desirable.

Other factors

It is clear from the discussion above that a variety of vasoactive substances (cytokines and growth factors) are implicated in the progression of CKD. These factors may be synthesized outside of the kidney and ultrafiltered in the glomerulus to act on tubular cells via apical receptors, or may be secreted by renal cells or infiltrating monocytes. The actions of these factors overlap often mediating the expression/release of or modulating the effect of other mediators; some of the better described factors are discussed here.

TGF-β is an important fibrogenic cytokine. Production is within the kidney and is stimulated by angiotensin II, high plasma glucose and IL-1 as well as by the mechanical stretching of mesangial and tubular cells. TGF-β favours apoptosis of podocytes, tubular epithelial cells and capillary endothelial cells, as well as ECM deposition and transdifferentiation of tubular cells into myofibroblasts [37]. Cytokines affected by TGF-β include plasminogen activator inhibitor 1 (PAI-1), hepatic growth factor, connective tissue growth factor and nitric oxide.

PAI-1 is not expressed in the normal kidney, expression is induced in kidney disease by angiotensin II and IV, by TGF-β and aldosterone. PAI-1 inhibits the normal degradation of ECM leading to abnormal matrix deposition leading to fibrosis. PAI-1 may also inhibit endothelial nitric oxide synthesis [38].

Nitric oxide functions as a vasodilator at physiological concentrations. It also inhibits mesangial cell proliferation and ECM synthesis and may limit capillary permeability, therefore inhibition of nitric oxide synthesis results in hypertension, proteinuria and tubulointerstitial fibrosis. Total nitric oxide production is low in CKD, an effect that is exacerbated by high parathyroid hormone levels, PAI-1, platelet-derived growth factor (PDGF), TGF-β and endothelin-1 all of which are over-expressed in CKD [2].

Expression of endothelin-1, 2 and 3 occurs in glomerular and tubular cells and is stimulated by angiotensin II, IL-1, TGF-β, hypoxia among others. Endothelins may play a role in progression of CKD by blocking nitric oxide synthesis, macrophage chemotaxsis and stimulation of interstitial fibroblast proliferation.

Aldosterone levels are often raised in CKD and induce oxidative stress, inflammation and fibrosis and impair endothelial nitric oxide synthesis [39].

Patient-specific factors

Race, male gender and age all have an adverse impact upon progression of CKD.

In a study of data drawn from the US census, the US renal data system and the NHANES study, black race (African-American) was demonstrated not only to be a risk factor for the development of hypertension but also of hypertension-related kidney disease including end-stage renal disease (ESRD) compared with non-black residents of the same age. Compared with women, men were shown to be at increased risk of hypertension and hypertension-related ESRD [40].

Multivariate analysis of the modification of diet in renal disease (MDRD) study showed that black race was an independent predictor of faster decline in GFR [42]. Multivariate analyses of the MRFIT (Multiple Risk Factor Intervention Trial) involving non-diabetic hypertensive men found an increased risk of ESRD among black patients [42]. The adverse effect of male gender and black race on the incidence and progression of CKD is reflected in the increased incidence and prevalence of these patients in renal replacement therapy programmes [43].

Renal function is lost with age, the average rate of loss of glomerular filtration being around 1 ml/min/year. Elderly patients have less 'reserve capacity' in their renal function, and thus greater susceptibility to the development of CKD with any given insult.

Several genetic factors also influence the progression of CKD. ACE gene polymorphism results in individuals with genotypes II, ID or DD depending on presence (I allele) or absence (D allele) of a fragment of the gene. The three genotypes are associated with low, intermediate or high circulating and intra-renal ACE (angiotensin-converting enzyme), respectively. The D allele (high ACE levels) has been demonstrated to have an adverse effect on progression of CKD [44].

A number of other genetic factors such as DNA single nucleotide polymorphisms may significantly influence the immune response, levels of inflammatory markers (IL-10, IL-6, TNF-α) and prevalence of atherosclerosis (apolipoprotein E, TGF, fetuin-A) in patients with CKD, all mechanisms by which disease progression is mediated [45].

Lifestyle factors

Smoking is a risk factor for the development of microalbuminuria, overt proteinuria and progression of renal disease in patients with type 1 and 2 diabetes [46–48] and has been associated with a greater risk of CKD progression in non-diabetic patients [49–52].

Proposed mechanisms of renal injury due to smoking include glomerular hyperfiltration and an increase in intra-glomerular capillary pressure, increased renin and angiotensin II production and increased albuminuria [53,54].

Obesity is not only a risk factor for the development of proteinuria and of CKD, but is also associated with accelerated progression of CKD [55,56]. Morbid obesity alone in the absence of primary renal disease may cause glomerular sclerosis [57]. Whilst weight loss has been demonstrated to reduce proteinuria in obese patients [58] conversely obesity provides an survival benefit in patients with severe (stage 5) CKD and so such strategies should be used with caution [59].

High dietary salt intake is associated with hypertension and increased cardiovascular disease [55]. Excess dietary salt intake also plays an important role in the progression of CKD that is independent of angiotensin II and systemic blood pressure. Salt activates the intra-renal vascular endothelium to produce TGF-β with resultant damage as described above [60].

Conclusion

The progression of early CKD is mediated by a common pathophysiology resulting in glomerulosclerosis and tubulointerstitial injury. Many of the factors associated with provoking this renal injury, and thus progression of CKD are associated with, or caused by, chronic kidney disease itself. By targeting therapies to try to break this vicious circle we can aim to slow or halt progression.

Reduction of intra-glomerular hypertension/hyperfiltration, systemic hypertension and proteinuria, ideally by blocking the role of angiotensin II and attention to hyperlipidaemia, acidosis and phosphate balance with lifestyle modification where appropriate can have a beneficial impact upon the progression of CKD.

Conflict of interest statement. None declared.

References

1. Eddy AA. Progression in chronic kidney disease. *Adv Chronic Kidney Dis* 2005; 12: 353–365
2. Yu HT. Progression of chronic renal failure. *Arch Intern Med* 2003; 163: 1417–1429
3. Hostetter TH, Olson JL, Rennke HG *et al*. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981; 241: F85–F93
4. Floege J, Alpers CE, Burns MW *et al*. Glomerular cells, extracellular matrix accumulation, and the development of glomerulosclerosis in the remnant kidney model. *Lab Invest* 1992; 66: 485–497
5. Rennke HG, Klein PS. Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. *Am J Kidney Dis* 1989; 13: 443–456
6. Kato H, Osajima A, Uezono Y *et al*. Involvement of PDGF in pressure-induced mesangial cell proliferation through PKC and tyrosine kinase pathways. *Am J Physiol* 1999; 277: F105–112
7. Novick AC, Gephardt G, Guz B *et al*. Long-term follow-up after partial removal of a solitary kidney. *N Engl J Med* 1991; 325: 1058–1062
8. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Eng J Med* 1984; 311: 89–93
9. Vora JP, Dolben J, Dean JD *et al*. Renal haemodynamics in newly presenting non-insulin dependent diabetes mellitus. *Kidney Int* 1992; 41: 829–835
10. Imanishi M, Yoshioka K, KonishiY *et al*. Glomerular hypertension as one cause of albuminuria in type II diabetic patients. *Diabetologia* 1999; 42: 999–1005
11. Serri O, Beauregard H, Brazeau P *et al*. Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependant diabetes. *JAMA* 1991; 265: 888–892
12. Hirschberg R, Brunori G, Kopple JD, Guler HP. Effects of insulin-like growth factor I on renal function in normal men. *Kidney Int* 1993; 43: 387–397
13. Anderson S, Vora JP. Current concepts of renal haemodynamics in diabetes. *J Diabetes Complicat* 1995; 9: 304–307

14. Hannedouche TP, Delgado AG, Gnionsahe DA *et al*. Renal haemodynamics and segmental tubular reabsorption in early type 1 diabetes. *Kidney Int* 1990; 37: 1126–1133
15. Keller G, Zimmer G, Mall G *et al*. Nephron number in patients with primary hypertension. *N Eng J Med* 2003; 348: 101–108
16. Rennke HG. How does glomerular epithelial cell injury contribute to progressive glomerular damage? *Kidney Int* 1994; 45: S58–S63
17. Rodriguez-Iturbe B, Johnson R, Herrera-Acosta J. Tubulointerstitial damage and progression of renal failure. *Kidney Int* 2005; 68: S82–S86
18. Savill JH. Regulation of glomerular cell number by apoptosis. *Kidney Int* 1999; 56: 1216–1222
19. Schelling JR, Cleveland RP. Involvement of Fas-dependent apoptosis in renal tubular epithelial cell deletion in chronic renal failure. *Kidney Int* 1999; 56: 1313–1316
20. Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 1984; 26: 861–868
21. Brazy PC, Stead WW, Fitzwilliam JF. Progression of renal insufficiency: role of blood pressure. *Kidney Int* 1989; 35: 670–674
22. Peterson JC, Adler S, Burkart JM *et al*. Blood pressure control, proteinuria, and the progression of renal disease. *Ann Intern Med* 1995; 123: 754–762
23. Burton C, Harris KPG. The role of proteinuria in the progression of chronic renal failure. *Am J Kidney Dis* 1996; 27: 765–775
24. Breyer JA, Bain RP, Evants JK *et al*. Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. *Kidney Int* 1996; 50: 1651–1658
25. Buckalew VM, Berg RL, Wang SR *et al*. Prevalence of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort. Modification of Diet in Renal Disease Study Group. *Am J Kidney Dis* 1996; 28: 811–821
26. Ruiz-Ortega M, Esteban V, Ruperez M *et al*. Renal and vascular hypertension-induced inflammation: role of angiotensin II. *Current Opinion Nephrol Hypert* 2006; 15: 159–166
27. Perico N, Codreanu I, Schieppati A, Remuzzi G. Pathophysiology of disease progression in proteinuric nephropathies. *Kidney Int* 2005; 67: S79–S82
28. Nankivell BJ, Boadle RA, Harris DC. Iron accumulation in human chronic renal disease. *Am J Kidney Dis* 1992; 20: 580–584
29. The GISEN group.Randomised placebo-controlled trail of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; 349: 1857–1863
30. Keane WF. Lipids and the kidney. *Kidney Int* 1994; 46: 910–920
31. Cases A, Coll E. Dyslipidaemia and the progression of renal disease in chronic renal failure patients. *Kidney Int* 2005; 68: S87–S93
32. Loghman-Adham M. Role of phosphate retention in the progression of renal failure. *J Lab Clin Med* 1993; 122: 16–26
33. Gimenez LF, Solez K, Walker WG. Relationship between renal calcium content and renal impairment in 246 human renal biopsies. *Kidney Int* 1987; 31: 93–99
34. Rossert J, Froissart M, Jacquot C. Anaemia management and chronic renal failure progression. *Kidney Int* 2005; 99: S76–S81
35. Nath KA, Hostetter KA, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 1985; 76: 667–675
36. Tang S, Sheerin NS, Zhou W *et al*. Apical proteins stimulate complement synthesis by cultured human proximal tubular epithelial cells. *J Am Soc Nephrol* 1999; 10: 69–76
37. Bottinger EP, Bitzer M. TGF-β. Signaling in renal disease. *J Am Soc Nephrol* 2002; 13: 2600–2610
38. Rerolle JP, Heritg A, Nguyen G *et al*. Plasminogen activator inhibitor type 1 is a potential target in renal fibrogenesis. *Kidney Int* 2000; 58: 1841–1850
39. Brown NJ. Aldosterone and end-organ damage. *Curr Opin nephrol Hypertens* 2005; 14: 235–241
40. Perneger TV, Klag MJ, Feldman HI, Whelton PK. Projections of hypertension-related renal disease in middle-aged residents of the United States. *JAMA* 1993; 269: 1272–1277
41. Hunsicker LG, Adler S, Caggiula A *et al*. Predictors of the progression of renal disease in the modification of diet in renal disease study. *Kidney Int* 1997; 51: 1908–1919
42. Klag MJ, Whelton PK, Randall BL *et al*. End-stage renal disease in African-American and white men: 16-year MRFIT findings. *JAMA* 1997; 277: 1293–1298
43. US Renal Data System.USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2004. *Am J Kidney Dis* 2006; 47[Suppl 1]: S1
44. Navis G, van der Kleij FGH, de Zeeuw D, de Jong PE. Angiotensin-converting enzyme gene I/D polymorphism and renal disease. *J Mol Med* 1999; 77: 781–791
45. Nordfors L, LindholmB, Stenvinkel P. End-stage renal disease – not an equal opportunity disease: the role of genetic polymorphisms. *J Intern Med* 2005; 258: 1–12
46. Chase HP, Garg SK, Marshall G *et al*. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA* 1991; 265: 614–617
47. McKenna K, Thompson C. Microalbuminuria: a marker to increased renal and cardiovascular risk in diabetes mellitus. *Scott Med J* 1997; 42: 99–104
48. Muhlhauser I, Overmann H, Bender R *et al*. Predictors of mortality and end-stage diabetic complications in patients with type 1 diabetes mellitus on intensified insulin therapy. *Diabet Med* 2000; 17: 727–734
49. Regalado M, Yang S, Wesson DE. Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension. *Am J Kid Dis* 2000; 35: 687–694
50. Stengel B, Couchoud C, Cenee S *et al*. Age, blood pressure and smoking effects on chronic renal failure in primary glomerular nephropathies. *Kidney Int* 2000; 57: 2519–2526
51. Orth SR, Stockmann A, Conradt C *et al*. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int* 1998; 54: 926–931
52. Ward MM, Studenski S. Clinical prognostic factors in lupus nephritis: the importance of hypertension and smoking. *Arch Intern Med* 1992; 152: 2082–2088
53. Halimi JM, Giraudeau B, Sylviane V *et al*. Effects of current smoking and smoking discontinuation on renal function and proteinuria in the general population. *Kidney Int* 2000; 58: 1285–1292
54. Orth SR. Effects of smoking on systemic and intrarenal hemodynamics: influence on renal function. *J Am Soc Nephrol* 2004; 15: S58–S63
55. Ritz E, Schwenger V. Lifestyle modification and progressive renal failure. *Nephrology* 2005; 10: 387–392
56. Hall JE, Crook ED, Jones DW *et al*. Mechanisms of obesity-associated cardiovascular and renal disease. *Am J Med Sci* 2002; 324: 127–137
57. Weisinger JR, Kempson RL, Eldridge FL, Swenson RS. The nephrotic syndrome: a complication of massive obesity. *Ann Intern Med* 1974; 81: 440–447
58. Morales E, Valerno MA, Leon M *et al*. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis* 2003; 41: 319–327
59. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; 63: 793–808
60. Sanders PW. Effect of salt intake on progression of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2006; 15: 54–60