An overview of recent advances in treating chronic kidney disease

Paul Roderick gives an overview of how the prevention, detection and treatment of chronic kidney disease (CKD) has changed in recent years. He explains why CKD has become a major health problem and the actions required to deal with this life-threatening disease.

■ chronic kidney disease ■ renal replacement therapy ■ trends ■ prevalence

In the last decade chronic kidney disease (CKD) has been recognized as a national and global health problem (Eknoyan et al, 2001). This paper outlines the reasons for this and recent policy responses in England. The emergence of the importance of CKD can be attributed to two major factors.

First, the renal registries documented the rising trend in acceptance (new take-on) rates onto renal replacement therapy (RRT)—dialysis or transplantation—in developed countries and the concomitant increase in the number of patients (Feest et al, 2005). Improving age-specific survival of patients on RRT also contributed to this rise. There is a substantial and disproportionate health-care cost of RRT and national projections estimate further rises in prevalence and cost.

The most plausible reason for the increase in acceptance rates was a greater liberalization of acceptance onto RRT and better detection and referral of older people with established kidney failure (EKF) rather than an increase in the underlying incidence of EKF. However, demographic changes (ageing population), reduction in competing risk from improved survival in cardiovascular disease (CVD) and increases in underlying determinants of CKD such as type 2 diabetes have contributed to the rise in the frequency of RRT (Munter et al, 2003). The cost effectiveness of RRT programmes has been limited by the shortage of kidneys for transplantation and the persistent problem of late referral. Such changes in RRT highlighted the need to understand the causes of CKD, how it could be prevented, how it could be identified earlier, how it could be managed in a more systematic manner to reduce CKD progression and CVD risk, and how to ensure earlier referral in those with advanced CKD.

The second major factor is the introduction of more accurate measures of kidney function than serum creatinine, which revealed that CKD was much more common than had been previously thought. Serum creatinine alone is an insensitive measure of kidney function because it is affected by creatinine production, largely from muscle, as well as by kidney excretion. Prediction equations estimated the glomerular filtration rate (eGFR) by taking into taken account factors associated with creatinine production such as age, gender and ethnic group. The most widely used has been the Modification of Diet in Renal Disease (MDRD) equation (Levey et al, 2005). A new definition of CKD was proposed by Kidney Disease Outcomes Quality Initiative (KDOQI), which enabled common reporting of CKD frequency across countries (National Kidney Foundation, 2002).

The KDOQI Group classified CKD into five grades of severity, termed stages (*Table 1*). This mirrors cancer classifications, although there is no inevitability about the progression of CKD. Evidence of disease must be shown over more than 3 months to establish chronicity.

Table 1. Staging of chronic kidney disease

Stage of CKD	Descriptor	eGFR ml/minute/1.73m^2	Urine microalbuminuria or other evidence of renal damage
1		90	+
2	Mild	60–89	+
3	Moderate	30–59	n/r
4	Severe	15–29	n/r
5	Established kidney failure	<15	n/r

n/r = not required

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The scale of the problem

Health surveys in several developed countries including Australia, Norway, Iceland and the US revealed a higher prevalence of CKD than previously thought. NHANES III, a nationally representative survey undertaken in the US in 1998–94, found the prevalence of CKD to be 4.7% for CKD 3–5 and overall 11% for CKD 1–5 (Coresh et al, 2003).

Some key positive associations with CKD—as measured by MDRD study (Coresh et al, 2003)—are age, gender, diabetes, and hypertension. The association of CKD with lower socio-economic status has become apparent (White et al, 2008). It is of interest that the prevalence of CKD is not higher in ethnic minority groups despite their higher incidence of RRT.

There have been no national surveys in the UK. Extrapolation from the Neoerica Study, which identified patients detected on routine serum creatinine measurement in primary care, suggested an expected prevalence of CKD stage 3–5 of 8.5%, which may have been an underestimate as those not having a serum creatinine blood test were assumed not to have had CKD 3–5 (Stevens et al, 2007).

Comparing NHANES III and IV (1999–2004), the prevalence of all stages of CKD in the US increased over the next decade. For ACR this was explained by a rising prevalence of obesity, diabetes and hypertension. The factors associated with eGFR changes were less apparent (Coresh et al, 2007).

The importance of prevention

The old adage 'prevention is a better than cure' is highly relevant to CKD. There is no cure for EKF. While transplantation for EKF is a more than cost effective mode of treatment compared to dialysis, there is still a significant risk of graft failure and the complications of lifelong immunosuppression. The burden of regular dialysis and the associated substantially reduced mortality are well recognized. CKD per se is an irreversible condition and there is a risk of progression to EKF. However, most people with CKD, especially older people, will not progress (John et al, 2007). Proteinuria and uncontrolled hypertension are key factors associated with progression (National Institute for Health and Clinical Excellence (NICE), 2008), and their central importance has been recognized in the Quality Outcomes Framework (QOF) for general practice renumeration as explained later in this article.

It is now clear that CKD is a strong independent risk factor for CVD which in absolute terms is a much greater risk than the risk of progression (Go et al, 2004). CVD risk is mediated both by classical risk factors such as hypertension and by non-classical factors such as endothelial damage and inflammation. There is a substantial research effort to understand the mechanisms, better predict CVD risk and to intervene more effectively to reduce risk. Finally, CKD *per se* is associated with increasing comorbidity as eGFR falls, which impacts on patients' quality of life—both physical and mental— and daily functioning (Chow et al, 2003). There are two major strategies for prevention:

- Primary: prevention of the occurrence of new cases of CKD
- Secondary: prevention of the progression of the natural course of CKD.

The potential importance of secondary prevention is shown by comparing CKD and RRT rates in Norway and the US. These countries have similar CKD prevalence but the risk of progression to RRT is 2.5 times higher in the US (Hallan et al, 2006).

First the CKD specific policy responses which address secondary prevention of CKD will be considered (Feehally et al, 2008).

Renal national service framework

The key national response in England was the publication of the Renal National Service Framework (NSF) Part 2 (Department of Health (DH), 2005). While the NSF addressed traditional policy concerns of dialysis and transplantation (DH, 2004), there were new sections in Part 2 on CKD, acute kidney injury (AKI) and alternatives to RRT (DH, 2005). For CKD there were two relevant quality requirements relating to prevention:

- Quality requirement 1—prevention and early detection of chronic kidney disease: *'People at increased risk of developing or having undiagnosed chronic kidney disease, especially people with diabetes or hypertension, are identified, assessed and their condition managed to preserve their kidney function.'*
- Quality requirement 2—minimizing the progression and consequences of chronic kidney disease. *'People with a diagnosis of chronic kidney disease receive timely, appropriate and effective investigation, treatment and follow-up to reduce the risk of progression and complications.'*

From these stemmed several initiatives relevant to CKD, e.g. eGFR reporting by all clinical biochemistry laboratories, NICE guidance on CKD (NICE, 2008), the inclusion of CKD in the QOF (The Health and Social Care Information Centre, 2009), and the Vascular Risk Assessment Programme (DH, 2008).

Reporting the estimated glomerular filtration rate

eGFR reporting was introduced into routine clinical biochemistry practice in 2006, and reports fed

back the MDRD derived eGFR value. Because of the inaccuracy of eGFR at higher levels of kidney function, it was only reported as >60 or >90 ml/minute/1.73m^2. The initial consequence was probably a significant increase in referrals to nephrologists, many probably being inappropriate. However, with the greater understanding of the interpretation of the eGFR measure and better clinical guidance this has stabilized.

It is important to recognize the limitations of the MDRD eGFR measure. At the individual level it is imprecise, especially when only one measure is used.It is biased especially at higher levels of eGFR where there is systematic underestimation of true eGFR, leading to an overestimation of CKD stage 3–5 (Levey et al, 2009). The MDRD formula was not validated on two key population groups, the very elderly or south Asians.

There have been important moves to reduce imprecision and bias by standardization and calibration of laboratory assays with a second MDRD formula based on isotope dilution mass spectrometry (IDMS) traceable serum creatinine—the gold standard.

There have also been controversies over the meaning of an eGFR <60 ml/minute/1.73m^2 (CKD 3–5) in the elderly, especially in the 45–60 age range. Most people identified with CKD are elderly, and epidemiological studies have shown that CKD is not inevitably progressive especially in the elderly (John et al, 2004). There is emerging evidence that a low eGFR is not a normal phenomenon as CKD is associated with increased risk of mortality and morbidity even in those over age 75 years, supporting the use of the term 'disease'—referring to an increased risk of symptoms, complications or adverse prognosis (Roderick et al, 2009).

Guidelines on CKD

The National Institute for Health and Clinical Excellence (NICE) produced guidelines on the identification, management and referral of adults with CKD in 2008, superseding UK consensus guidelines published in 2005 (NICE, 2008). A key outcome was the recognition that CKD is a condition that should be largely managed in primary care with referral to nephrologists limited to those with more advanced CKD or progressive CKD. Salient recommendations were:

- CKD measurement—guidelines supported the use of MDRD, and suggested the classification of CKD stage 3 be subdivided into 3a and 3b and presence of proteinuria in later stages to be noted with a 'p' suffix
- No population screening for CKD nor screening by age, gender or ethnic groups, partly because the yield of CKD that is likely to progress to EKF is low
- Targeted testing of eGFR and albuminuria in groups at higher risk of CKD who are already under clinical care. These are not to be formal screening programmes but largely form part of chronic disease management in primary care. Key groups to be targeted are patients with:
  - Diabetes
  - Hypertension
  - Cardiovascular disease
  - Structural renal tract disease, renal calculi or prostatic hypertrophy
  - Multisystem diseases with potential kidney involvement (e.g. systemic lupus erythematosis)
  - Family history of stage 5 CKD or hereditary kidney disease.
- Offer of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) to non-diabetic people with CKD and hypertension and ACR ≥30 mg/mmol (approximately equivalent to PCR ≥50 mg/mmol, or urinary protein excretion ≥0.5 g/day)
- Effort focussed particularly on those in whom a decline of GFR continuing at the observed rate would lead to the need for RRT within their lifetime by extrapolating the current rate of decline
- The aim in people with CKD should be to keep the systolic blood pressure <140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure <90 mmHg.
- Referral for specialist assessment in the following circumstances:
  - Stage 4 and 5 CKD (with or without diabetes)
  - Higher levels of proteinuria (ACR ≥70 mg/mmol, approximately equivalent to PCR ≥100 mg/mmol, or urinary protein excretion ≥1 g/day) unless known to be due to diabetes and already appropriately treated
  - Proteinuria (ACR ≥30 mg/mmol, approximately equivalent to PCR ≥50 mg/mmol, or urinary protein excretion ≥0.5 g/day) together with haematuria
  - Rapidly declining eGFR (>5 ml/minute/1.73 m^2 in 1 year, or >10 ml/minute/1.73 m^2 within 5 years)
  - Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses
  - People with, or suspected of having, rare or genetic causes of CKD

Table 2. Modifiable factors of chronic kidney disease (CKD)

■ Type 1 or 2 diabetes
■ Primary hypertension
■ Low birth weight
■ Smoking
■ Obesity/metabolic syndrome
■ Causes of urinary obstruction or reflux
■ Modifiable/preventable factors associated with secondary glomerulnephritides (e.g. certain infections)
■ Cardiovascular disease
■ Nephrotoxin exposure (occupational, environmental and drug)

There is a large overlap with the underlying causal conditions for vascular disease.

■ Suspected renal artery stenosis.

General practice quality and outcomes framework

CKD indicators were introduced to the QOF for general practice renumeration in 2006/2007 and have enabled more systematic identification of and intervention in patients with CKD. The key interventions following guidance above are blood pressure control and specific use of renin angiotensin system (RAS) inhibitors in those with proteinuria.

There are now incentives for general practice to develop registers of patients with stage 3–5 CKD and indicators for blood pressure and ACR measurement, blood pressure control and use of ACE and ARBs. These indicators are being reviewed and updated annually. The role of RAS inhibition in patients with non-diabetic microalbuminuria is not clear and remains a research issue.

Results from QOF 2008/9 show that virtually all practices have a register of CKD (The Health and Social Care Information Centre, 2009):

- 3.5% of the population had been identified with stage 3–5 disease
- 98% of identified patients had had their blood pressure measured in the past 15 months
- 73% of non-excepted patients had a blood pressure of ≤140/85 mmHg
- 87% of non-excepted patients with hypertension and proteinuria were treated with ACE and ARB drugs.

These data indicate considerable progress in establishing registers and data recording but some improvement is still needed with regard to blood pressure control in CKD.

The CKD database does not allow individual-based reporting so one cannot break these down by age or comorbidity.

Avoidance of AKI in those with pre-existing CKD is not a feature of QOF but is a significant issue cutting across all specialties. Better recognition of patients with CKD may avoid insults which precipitate AKI (e.g. avoiding nephrotoxic drugs).

Vascular risk assessment programme

The Vascular Risk Assessment Programme is now being implemented in England (DH, 2008). The aim is for all adults aged 40–74 years to have vascular risk assessments and stepped interventions according to their level of risk. It will include testing for CKD in those groups at higher risk such as patients with newly diagnosed hypertension. This is an ambitious programme and it remains to be seen how well it is implemented and its effect on future vascular events. Interventions to stop smoking and reduce weight if obese or overweight are very important in CKD as they will reduce CVD risk and may contribute to reducing CKD progression.

Recent changes in RRT rates

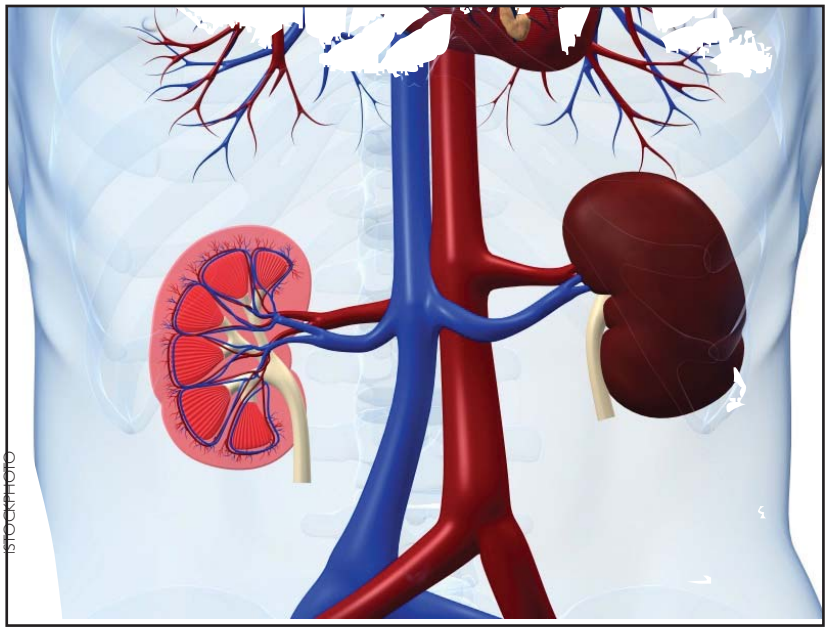
Data from the UK Renal Registry for 2007 show that there was continued growth of about 5% per annum in RRT patients in England from 2002 to 2007 (Ansell et al, 2008). Acceptance rates dipped in 2007 to 107 per million population but there is an underlying upward trend. Most significantly was the fall in the proportion of patients referred late (under 3 months before needing RRT) in four units with fairly complete data—from 31% in 2002 to 21% in 2007—and a concomitant increase in those referred over 1 year before start.

It is not clear yet to what extent this is due to the impact of the policies just outlined. Expansion of alternatives to dialysis will contribute to changes in the elderly.

Primary prevention

To prevent the occurrence of new CKD one must target potentially modifiable causes of CKD—not non-modifiable factors such as age, gender, ethnicity and genetics. Modifiable factors are listed in *Table 2*.

The 'Western way of life' is deleterious to kidney function. Promoting healthy lifestyles for people in England and Wales is an important national priority. For obesity there is a national strategy—*Healthy Weight, Healthy Lives: A Cross-Government Strategy for England* (DH, 2008) and the recent launch of the Change4life programme which attempts to encourage healthy behaviours in children with respect of diet and exercise. In future years this will



The incidence of chronic kidney disease may be rising due to the obesity epidemic.

hopefully impact on obesity or the incidence of type 2 diabetes rates, thereby reducing incident CKD. Other primary prevention measures are:

- Efforts to stop people starting smoking or to encourage quitting in those without pre-existing CKD—supported by major DH initiatives on developing NHS quitting services and smoke free public places
- Treatments to prevent the microvascular and macrovascular complications of both types of diabetes, e.g. by glycaemic control and blood pressure control. There is NICE guidance on both type 1 and 2 diabetes (National Collaborating Centre for Chronic Conditions (NCCC, 2008). The specific role of RAS inhibition in primary prevention of kidney damage is unclear. Early detection of type 2 diabetes by screening will be part of the new National Vascular Risk Assessment Programme
- Prevention, detection and effective control of hypertension. There are NICE guidelines on hypertension (NCCC, 2006). Efforts to reduce salt consumption, enhance physical activity and prevent obesity will all help to reduce hypertension.

Key points

- Chronic kidney disease is common especially in older people
- It is associated with an increased risk of cardiovascular disease and, if it progresses, the consequences of kidney failure and a eventually need for renal replacement therapy (dialysis or transplantation)
- Renal replace therapy is costly and demand is rising
- Primary and secondary prevention of CKD are both important goals
- Several policy initiatives have promoted better secondary prevention including earlier detection (eGFR reporting, the Vascular Risk Assessment Programme) and better management of CKD (Quality and Outcomes Framework)

Some developments

The new formula CKDEpi has been derived which reduces some of the problems with MDRD and is more accurate at higher levels of true GFR. It is likely to be introduced. One consequence will be a lower prevalence of CKD 3–5.

The international CKD classification is likely to be amended to take account of albuminuria even when eGFR is >60 ml/minute/1.73 m^2 and to split the prognostically heterogeneous stage 3 category into two subgroups 3a and 3b.

Routine measurement of serum creatinine and urinary albumin and creatinine in the national Health Surveys for England (HSE) 2009 and 2010 will give national prevalence data of all stages, albeit based on single measures of both. Data from HSEs from 2003 to 2005, which have enhancement for ethnic minorities and the elderly, will permit estimation of expected prevalence of CKD at primary care trust level and estimation of changes in CKD prevalence over time.

Conclusions

CKD is a common chronic condition associated with poor outcomes. Incidence is probably rising in developed countries largely as a consequence of the obesity epidemic. Effective primary prevention strategies are urgently needed to stem this rise. Since the renal NSF, a number of initiatives have been introduced in England to enhance the secondary prevention of CKD, with a greater focus on the role of primary care. Identification and treatment of CKD has improved, although blood pressure control remains suboptimal, and better integration is needed with associated chronic conditions. The impact of these policies on the consequences of CKD—premature mortality, progression to EKF and CVD—is as yet unknown, and there remain uncertainties about how to deal with CKD in older people who have the highest CKD prevalence. JRN

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