The estimated glomerular filtration rate in primary and secondary care

Most biochemistry laboratories in the UK are now reporting estimated glomerular filtration rate (eGFR) routinely in conjunction with serum creatinine, as part of a major initiative to improve the detection and management of chronic kidney disease (CKD) in primary care. This has led to an increase in referrals to nephrology services, often following routine screening of at-risk groups. This editorial discusses the reasons why eGFR is now being reported to primary care doctors, reviews the advantages and disadvantages of this development, and considers the implications for the future management of CKD.

What has driven eGFR reporting?

CKD is an extensive health problem with important implications for sufferers and their carers. John et al (2004) estimated the prevalence of moderate to severe CKD as 5500 per million population with as many as 85% unknown to renal services. The incidence in the UK is rising because of the ageing population, and an increasing prevalence of high-risk diseases (e.g. diabetes and hypertension), especially among ethnic minority groups. The annual incidence of patients starting dialysis is about 100 per million population, and the prevalence of renal replacement therapy (dialysis and transplant) is 700 per million population (Renal Association, 2006). The dialysis population is predicted to grow for at least 25 years (Roderick et al, 2004). This will have a great financial impact – the annual cost of hospital haemodialysis is as high as £20 000 per patient.

The cardiovascular risk conferred to CKD patients is a major health problem. Any level of CKD carries an increased risk, but the risk increases with severity of disease such that a 30-year-old on dialysis has the same risk of cardiovascular death as an 85-year-old without kidney disease. Advanced renal failure brings other important complications such as anaemia and bone disease, which carry significant morbidity and mortality.

Progression of CKD can be attenuated by strict blood pressure control, renin–angiotensin blockade, and attention to lipid profile, smoking and obesity. However, as CKD rarely becomes symptomatic until renal function has declined significantly, earlier detection is essential, a message conveyed in the *National Service Framework for Renal Services* (Department of Health, 2005).

The Renal Association (2005) published evidence-based guidelines aimed at improving the detection, monitoring and management of CKD in primary care with specific criteria of when to refer to secondary care. These guidelines adopted the US classification of CKD (National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2002) which describes five stages depending on the eGFR (*Table 1*). It was thus recommended that biochemistry laboratories should routinely report eGFR alongside serum creatinine to primary care doctors.

By measuring eGFR and urinary protein in all high-risk individuals (e.g. diabetics, hypertensives, cardiac disease, peripheral vascular disease, long-term users of non-steroidal anti-inflammatory drugs, angio-tensin-converting enzyme inhibitors, calcineurin inhibitors and other nephrotoxins, those at risk of obstructive nephropathy) it is hoped that detection of CKD will improve. The Quality and Outcomes Framework provides additional incentive with financial reward for GP services performing well against surrogate markers of quality care such as blood pressure and cholesterol monitoring, treating blood pressure to target and registering all CKD patients.

Table 1. Classification of chronic kidney disease according to glomerular filtration rate (GFR)

Stage	GFR (ml/min)
Stage 1	Kidney damage with GFR>90
Stage 2	Kidney damage with GFR 60–89
Stage 3	Kidney damage with GFR 30–59
Stage 4	Kidney damage with GFR 15–29
Stage 5	Kidney failure <15 or on dialysis

From National Kidney Foundation Kidney Disease Outcomes Quality Initiative (2002)

What is eGFR and why is it better than serum creatinine?

Exact measures of GFR using markers such as inulin, EDTA and iothalamate are time-consuming, expensive and impractical to use routinely when assessing kidney function. Creatinine clearance has good correlation with real GFR, but this requires a 24-hour urine collection and serum creatinine, so is time-consuming, inconvenient and subject to collection error. Serum creatinine is traditionally used to detect renal dysfunction but its biological properties make it inaccurate: it is directly proportional to muscle mass and creatinine is secreted, as well as filtered, by the kidney. A patient with normal serum creatinine may still have reduced GFR. Moreover a small rise in serum creatinine in the early stages of CKD may reflect a significant decline in renal function.

To overcome these problems, formulae have been developed that estimate the GFR taking into account the serum creatinine and factors that predict the muscle mass. The widely used Cockroft–Gault formula uses serum creatinine and weight to estimate GFR. This formula has many uses, and is still widely used to calculate drug dosing. However, in CKD it has two drawbacks – first, it is validated in subjects with normal renal function and its accuracy is highest in these groups, whereas the health implications of CKD require accuracy at lower levels of GFR, and second it uses weight (supplying a reliable and up-to-date weight measurement to a remote location such as a biochemistry laboratory to perform the calculation is difficult). In contrast, the four variable Modified Diet in Renal Disease (MDRD) equation was validated in patients with CKD stage 3 or worse, and requires only demographic data for its calculation (Levey et al, 1999).

Using this method one can expect 90% of eGFRs to be within 30% of the true GFR at GFRs <60 ml/min/1.73m^2. Based originally on a predominantly white, non-diabetic population, it has since been shown to accurately predict GFR in other groups such as African Americans and diabetics (Lewis et al, 2001; Poggio et al, 2005).

Nevertheless, eGFR using the creatinine-based MDRD formula can be misleading in several situations: extremes of age, unusual body composition (amputees, muscle wasting), oedematous states and pregnancy. As a one-off measure it has no value in acute renal failure where GFR is declining rapidly. Also, the MDRD equation performs poorly at high GFRs, systematically underestimating GFR in healthy individuals (Rule et al, 2004).

Potential problems in using eGFR to detect kidney disease

The advantage of reporting eGFRs is that no longer will apparently normal serum creatinine lead to missed diagnosis of CKD. However, used alone, eGFR will not detect important types of patient with kidney disease. Early diabetic nephropathy is characterized by hyperfiltration with high or normal GFR and microalbuminuria. Early treatment with inhibitors of the renin–angiotensin system in diabetics with proteinuria prevents progression of nephropathy in type 1 and type 2 diabetics (Brenner et al, 2001; Parving et al, 2001; IDNT Group, 2001). Many patients with other causes of glomerular disease also have normal GFR and significant proteinuria, and most will benefit from blood pressure reduction and angiotensin-converting enzyme inhibition or angiotensin blockade. The Renal Association (2005) guidelines suggest routine urine dipstix testing in addition to eGFR in high-risk groups.

There may be a tendency to 'over-detect' and label patients as having disease where none exists. CKD stages 1 and 2 require other evidence of chronic kidney damage: persistent microalbuminuria, proteinuria and/or microscopic haematuria (after exclusion of other urological causes), structural abnormalities on ultrasound such as polycystic kidneys and biopsy-proven glomerulonephritis (Renal Association, 2005).

GFR has a natural tendency to decline with age, although there is evidence that much of the age-related decline in renal function is related to hypertension and therefore may have a pathological basis (Lindeman et al, 1984). Using the new criteria of CKD stage 3 (eGFR 30–59 ml/min/1.73m^2), as many as 30% of people over the age of 75 years have CKD stage 3 (Cirillo et al, 2006). However, most people with CKD stage 3 will not develop symptoms of renal failure and only a very small proportion will require renal replacement therapy (Eriksen and Ingebretsen, 2006). There is great potential to over-investigate and over-treat these patients, causing anxiety to the patients and strain on resources.

Conclusions

Routine reporting of eGFR is one of several measures which should improve detection of CKD in primary care. Early detection should enhance the cardiovascular risk management of many and prevent large numbers of patients from requiring renal replacement therapy (by slowing disease progression). Patients with advanced renal dysfunction will be identified sooner, allowing appropriate management of renal anaemia and bone disease, and timely preparation for dialysis.

However, using only eGFR to diagnose CKD stage 3 would significantly overestimate the prevalence of CKD, especially in the elderly population, and would run the risk of further adding to the workload of primary care and secondary renal services, without necessarily improving patient outcomes. **BJHM**

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

Cirillo M, Laurenzi M, Mancini M, Zanchetti A, Lombardi C, De Santo NG (2006) Low glomerular filtration in the population: Prevalence, associated disorders, and awareness. *Kidney Int* **70:** 800–6

Department of Health (2005) *The National Service Framework for Renal Services Part Two: Chronic Kidney Disease, Acute Renal Failure and End of Life Care.* Department of Health, London

Eriksen BO, Ingebretsen OC (2006) The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age. *Kidney Int* **69:** 375–82

IDNT Group - The ACE Inhibitors in Diabetic Nephropathy Trialist Group (2001) Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* **134:** 370–9

John R, Webb M, Young A, Stevens PE (2004) Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis* **43**(5): 825–35

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, for the Modification of Diet in Renal Disease Study Group (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* **130:** 461–70

Lewis J, Agodoa L, Cheek D et al (2001) Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. *Am J Kidney Dis* **38**(4): 744–53

Lindeman RD, Tobin JD, Shock NW (1984) Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* **26**(6): 861–8

National Kidney Foundation Kidney Disease Outcomes Quality Initiative (2002) *Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation Classification and Stratification.* National Kidney Foundation, New York

Parving HH, Lehenert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* **345:** 870–8

Poggio E, Wang X, Greene T, Van Lente F, Hall P (2005) Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* **16:** 459–66

Renal Association (2005) *Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral.* Renal Association, Hampshire

Renal Association (2006) *UK Renal Registry Ninth Annual Report.* Renal Registry, Bristol

Roderick P, Davies R, Jones C, Feest T, Smith S, Farrington F (2004) Simulation model of renal replacement therapy: predicting future demand in England. *Nephrol Dial Transplant* **19:** 692–701

Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG (2004) Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* **141:** 929–37

KEY POINTS

- Estimated glomerular filtration rate will allow categorization of patients into five stages of chronic kidney disease.
- Diagnosis of chronic kidney disease stages 1 and 2 requires demonstration of other markers of kidney disease (e.g. proteinuria), in addition to reduced estimated glomerular filtration rate.
- Early detection of chronic kidney disease and treatment with angiotensin-converting enzyme inhibitors or angiotensin blockers gives an opportunity to prevent progression of kidney disease and reduce associated cardiovascular morbidity and mortality.