Welcome to the era of CKD and the eGFR

Estimating glomerular filtration rate using a simplified formula will lead to a vast increase in detection of chronic kidney disease in Australia

In patients with chronic kidney disease (CKD), the degree of reduction in the glomerular filtration rate (GFR) is closely linked to the development of complications of CKD, and GFR is the best index for classifying the severity of the disease. In 2002, a US working party produced a five-stage classification of CKD, with guidelines for management according to stage, based largely upon GFR (Box).[1] The classification is logical and simple and has enjoyed worldwide endorsement. However, one problem has impeded widespread usage of the classification — most clinicians do not measure or calculate GFR.

Why estimate GFR?

The gold standard for measurement of GFR is kidney clearance of inulin, but this method is a research tool and not practical for clinical practice. GFR may be accurately measured by determining the clearance rate of exogenous radioisotopes, such as radiolabelled Cr^{51}-EDTA. Alternatively, the measurement of 24-hour creatinine clearance provides a reasonable, though less accurate, approximation. Both methods are inconvenient, time-consuming and costly. Serum creatinine concentration is widely used as a surrogate marker of GFR, but is crude and insensitive. For example, among the nationally representative AusDiab cohort of 11 247 Australian adults, 1.1% had elevated serum creatinine levels whereas 11.2% had a calculated GFR < 60mL/min.[2]

Because of these anomalies, much effort has been directed at deriving formulas that use serum creatinine level together with other clinical variables, such as age, sex and weight, to yield an accurate estimated GFR (eGFR). The abbreviated MDRD (Modification of Diet in Renal Disease) formula for deriving eGFR has been extensively validated in US populations and is endorsed for the classification of CKD.[1] The inputs required for the (predominantly white) Australian population are serum creatinine level, age and sex (the performance of the formula is less satisfactory among people of Chinese origin,[3] and thus possibly others of Asian ethnicity, and is untested among Indigenous Australians). Thus, all data required for calculating eGFR using the abbreviated MDRD formula are currently provided on the typical pathology request form, making automated reporting of eGFR potentially feasible.

The growing burden of CKD

The burden of CKD has long been underappreciated. Stage 5 CKD (end-stage kidney disease [ESKD]), which requires dialysis or transplantation to prevent death from kidney failure, provides the most obvious burden of CKD, as dialysis and transplantation are highly visible and enormously costly health problems.

Earlier stages of CKD are more prevalent and may be even more costly than ESKD. Projections based on data from the AusDiab survey suggest that 1.4 million Australian adults (11.4% of the non-institutionalised population) had CKD stages 3–5 in 2000.[2] Of these, 11 660 (< 1%) were living on dialysis or a functioning kidney transplant.[4] For the 99% with CKD who were not receiving dialysis or had not had a transplant, two major consequences have become apparent: increased risk of developing ESKD and increased cardiovascular risk compared with the normal popula-

K/DOQI classification of chronic kidney disease[1]

CKD stage	Definition	Prevalence in Australian adults[2]
1	Kidney damage (albuminuria, haematuria or abnormal kidney imaging), eGFR > 90 mL/min	0.9% (n = 112 000)
2	Kidney damage, eGFR 60–90 mL/min	2.0% (n = 250 000)
3	Moderate kidney failure, GFR 30–59 mL/min	10.9% (n = 1 400 000)
4	Severe kidney failure, GFR 15–29 mL/min	0.3% (n = 40 000)
5	End stage kidney disease requiring dialysis or transplant, GFR < 15mL/min	0.1% (n = 13 000)

CKD = chronic kidney disease. eGFR = estimated glomerular filtration rate. K/DOQI = Kidney Disease Outcomes Quality Initiative. ◆

tion. Both of these risks are associated with a progressive increase in mortality rate through successive stages of CKD, as was demonstrated in a longitudinal study of subjects in a large health maintenance organisation in the United States (figures represent 5-year mortality rates): no CKD, 10.2% ± 0.5%; stage 2, 19.5% ± 1.9%; stage 3, 24.3% ± 0.8%; stage 4, 45.7% ± 3.5%.[5] Indeed, overwhelming evidence now shows that CKD is an independent risk factor for cardiovascular disease and should be added to the list of "traditional" risk factors.[6]

The need to identify CKD

Identifying cases of CKD may help to prevent ESKD and the attending increase in cardiovascular morbidity and mortality. There is clear evidence that intervention may slow the rate of decline in GFR for people with CKD, particularly if identified at an early stage. Blood pressure control, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists for patients with proteinuric nephropathies, blood sugar control and regular clinical follow-up are all proven to be of benefit.[7] Reduction in the cardiovascular burden associated with CKD through aggressive management of traditional and non-traditional (eg, elevated calcium phosphate product) cardiovascular risk factors appears likely to be effective, although definitive studies are awaited.

CKD is generally asymptomatic. Subject awareness at all stages other than stage 5 is almost non-existent, and clinician awareness is similarly low.[8] Thus, detecting CKD requires GFR measurement or estimation.

In this issue of the Journal (*page 138*), a working group representing the peak bodies of Australian nephrology, pathology and biochemistry plus Kidney Health Australia has proposed that eGFR be automatically calculated whenever a serum creatinine measurement is requested through any pathology service in Australia. The eGFR will be reported whenever the value is < 60 mL/min, enabling classification of the patient within CKD stages 3–5. Values above 60 mL/min will not be reported, because of inaccuracies in eGFR in that range and because the complications of CKD are mainly seen at GFR < 60 mL/min. The program will include a comprehensive, ongoing strategy for quality control of laboratory serum creatinine measurements, as this is critical to the accuracy of eGFR, and a major education campaign designed to provide clinicians with guidance on interpreting eGFR and managing CKD.

This initiative may prove to be incredibly important if Australia is to limit the current escalation in the burden of CKD. One crucial aspect will be to determine whether automated reporting of eGFR and early detection of CKD result in better health outcomes for the general population, by formally assessing the impact on the health system and individuals before and after the recommended change in eGFR reporting.

As with any bold undertaking, there are certain risks and limitations. Firstly, an enormous number of patients will be identified, particularly among elderly Australians. The AusDiab study suggests the majority of patients with stage 3 CKD will be elderly women.[2] The natural history of CKD in older people is poorly understood, as is the difference between the impact of normal ageing versus disease on GFR. The potential for increased costs to the health care system through an increase in tests, prescriptions and referrals to nephrologists may be significant, and the potential benefits are uncertain. The increase in workload for nephrologists, in particular, may be unsustainable. Education of clinicians will be crucial here, as will further research into the natural history of CKD in older people.

Secondly, although eGFR is well validated for adult whites, caution will be required in applying eGFR to other patient groups such as Indigenous Australians and people of Asian origin.[3]

Finally, clinicians must not fall into the trap of interpreting an eGFR of > 60mL/min as indicative of healthy kidney function. While GFR is the best overall measure of kidney function and therefore the dominant determinant of the stage of CKD, for people at risk of kidney disease, testing for other markers of kidney damage — such as hypertension, haematuria, abnormal structure and, most importantly, albuminuria/proteinuria — must not be forgotten.

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The glomerular ltration rate (GFR) measures how much plasma the kidneys lter in one minute. In principle, this can be calculated by measuring the amount of a substance that appears in the urine over a given amount of time and the concentration in the blood (for substances with a constant concentration) or the rate of disappearance from the blood (for exogenous substances). The ideal substance for this measurement should be freely ltered at the glomerulus, and not reabsorbed or excreted by the rest of the nephron. Several exogenous substances that full these criteria have been identied, includi... The early identification of chronic kidney disease (CKD) is a legitimate enterprise if it provides meaningful opportunities for effective and safe interventions that reduce the risk of death, end-stage renal disease, or complications of renal dysfunction. The screening of unselected populations not already known to be at risk of CKD has the potential of harm and has not been shown to be cost-effective. The application of formulas for the estimation of GFR (eGFR) to the guidelines for staging of chronic kidney disease (Kidney Disease Outcomes Quality Initiative, K/DOQI) as universal screening tools is of dubious value and has inherent dangers. Concomitant type 2 diabetes and chronic kidney disease (CKD) increases the risk of heart failure (HF). Recent STUDIES: demonstrate beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on CKD progression and HF hospitalization in patients with and without diabetes. In addition to inhibiting glucose reabsorption, SGLT2i reduce proximal tubular sodium reabsorption, possibly leading to transient natriuresis. the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation in 2012.6 The great success of the Australasian Creatinine Consensus Working Group subsequently has driven similar efforts looking. at the standardization of measurement and reporting of urinary protein.7. With implementation of the KDOQI CKD deni-tion and staging and automatic reporting of eGFR, the need to educate family physicians in the recognition and management of patients with CKD was immedi-ately apparent.Â Welcome to the era of CKD and the eGFR. Med J Aust. 2005;183(3):117-118.