Detection and progression of chronic kidney disease: does the rear-view mirror help?

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Fuelled by the pandemic of obesity and Type 2 diabetes mellitus, the prevalence of chronic kidney disease (CKD) is a major global health burden. Its prevalence in many continents already affects over 10% of the adult population. Between Europe and the United States, approximately 1 million patients currently require renal replacement therapy (RRT), including dialysis and transplantation. By 2030, it is estimated this figure will exceed 2 million [1–3]. These figures are disconcerting: the cost of managing end-stage renal disease (ESRD) and its attendant co-morbidities even today engulfs a disproportionate percentage of the health dollar and, if the above estimates are even partly correct, it is a cost which will soar in forthcoming years. However, the cost of renal disease does not commence simply when the patient reaches end-stage. With the number of pre-end-stage CKD patients estimated at >30-fold those requiring RRT, the overall drain on economic and health resources is exceptionally high, even—perhaps particularly—for those who do not eventually reach ESRD [4].

Both the numbers and costs highlight a pressing need to successfully screen and identify patients with CKD, and to define those most at risk of progression. The first, to interpret national and global health patterns as they evolve; and the second, to effect a delay in functional renal deterioration. The overwhelming challenge even for developed societies is that the numbers defy traditional attempts at targeted appraisal and intervention. However, the task is not hopeless. Several recent studies suggest that if CKD can be identified, it might be possible to slow or even prevent a fall in renal function, at least for a limited time in targeted populations exposed to intense, often novel, models of care [5–7].

Effective screening ideally requires simple, precise and affordable markers. Those that currently define CKD are the estimated glomerular filtration rate (eGFR), based on the serum creatinine and, in the initial stages, urinary protein. It is likely that future prevalence studies will incorporate proteinuria more widely as it is a strong and independent predictor of progressive functional decline [8, 9]. Nevertheless, neither its definition nor its method of detection is free from controversy. The commonly-used reagent strip or ‘dipstick’ analysis is subject to the substantial error: the reagent pads are variably sensitive (according to the manufacturer) and individual
readings can be misinterpreted particularly when the urine (and therefore the urinary protein) is highly concentrated [10]. More quantitative estimates of total proteinuria, purportedly measuring albumin and other protein, have a strong empirical base of guiding treatment algorithms for disease, based on 24-h estimates. However, measurement of ‘total’ proteinuria can be flawed by low protein concentration, aminoglycoside antibiotics, haematuria, methodological inconsistencies between laboratories and, particularly, lack of sensitivity in diabetic patients. At urinary protein concentrations well within the normal range, modestly elevated concentrations of albuminuria in diabetics are associated with a raised CKD and mortality risk [11]. Urinary albumin might also be a more sensitive marker of glomerular pathology in other conditions such as hypertension and systemic sclerosis [12, 13].

Interpretation of renal function based on serum creatinine has been subject to a range of modifying equations since the emergence of the Cockcroft-Gault equation over 35 years ago. Recent studies have compared the CKD-Epidemiology Collaboration (CKD-EPI) equation with its immediate precursor, the Modification of Diet in Renal Disease (MDRD) equation. Initial appraisal suggests that the former is both more precise and valid across a larger functional range of eGFR [14]. In particular, the CKD-EPI equation is able to identify participants in clinical studies with an eGFR of up to 120 mL/min/1.73 m² compared with the MDRD, whose accuracy was limited to an eGFR <60 mL/min/1.73 m². The effect has been a more realistic appraisal of renal function, at least for people up to the age of 70 years. For example, in the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study, the percentage of women with Stage 3 CKD fell from 8 to 5% when the CKD-EPI equation was used. However, whatever equation is used, it must be remembered it can only be an estimate, whose validity is assumed to be integrated related to a population. The effect of individual variables such as meat intake, muscle mass, race or advanced age cannot be assumed to be integrated—a fact often overlooked by clinicians and reporting laboratories alike.

Identifying risk factors for the progression of CKD is an important strategy to target those most likely to benefit from specific intervention. Together with primary prevention, it is one of the only effective tools to combat a pandemic whose progression, unusually, is measured in years rather than days or weeks. This insidious rate of progression and the difficulty in identifying the particular candidates within the community most likely to deteriorate, continue to challenge effective treatment paradigms. Nevertheless, community and mass screening studies over the past decade have shown potential benefit from early detection and intervention [15–17], and a recent, randomized community-based study validated a nurse-coordinated model of care in a low-risk cohort [18]. Thus, any method that helps to identify those most at risk and can be clinically applied has merit, bearing in mind that the strength of such studies lies in trends and associations rather than understanding pathophysiological mechanisms.

Turin et al. [19] report the utility of adding a second eGFR assessment within a 12-month period to assess the progression of CKD; in particular, whether a second measure added power to the model. This retrospective study examined an adult population from the Alberta Kidney Disease Network data repository between 1 May 2002 and 31 March 2008, with follow-up to 31 March 2009 to ensure at least 12 months enrolment in all patients. Excluding Stage 5 CKD and those with frequent (>24) measures, the authors analysed 598 397 patients who had two or more creatinine measurements in 1 year, separated by at least 6 months. They examined the percentage change in eGFR (calculated using the CKD-EPI equation), grouped as ‘Certain drop’ (fall in CKD category with ≥25% decrease in eGFR); ‘Uncertain drop’ (fall in CKD category with ≤25% decrease); ‘Stable’ (no change in CKD category); ‘Uncertain rise’ and ‘Certain rise’—as the inverse of the first two categories. Of the total, 74.8% of patients were stable, 3.3% (19 591) had a certain drop and 3.7% (22 171) had a certain rise in kidney function.

The outcome measure was development of ESRD. There were 1966 (0.3%) ESRD events over a median follow-up of 3.5 years. Unadjusted rates were highest for those with a certain drop in kidney function (rate 6.79 per 1000 person-years; 95% CI 6.77–6.81). Adjusted for the first (baseline) eGFR measurement, the highest rate was also in the ‘Certain drop’ group (rate 0.77; 95% CI 0.44–1.10) but—and like comparable studies [20–21]—after adjustment for the second eGFR assessment, the highest rate of ESRD development was in the ‘Certain rise’ group (rate 0.61; 95% CI 0.60–0.63). Similar, counter-intuitive findings were evident on all analyses. When compared with participants with stable kidney function, the increased risk for both ‘Certain fall’ and ‘Certain rise’ groups was evident after covariate adjustment at the first but not the last eGFR measurement. A spline analysis examining the relationship between the per cent change in the eGFR as a continuous variable and risk of ESRD increased in a near exponential fashion except when the second eGFR measurement was included as a variable. The authors suggest that extrapolation of a 1-year decline in kidney function did not add information regarding the risk of ESRD beyond that of the last measurement of eGFR alone.

The strengths of the study lie especially in the numbers of community-dwelling subjects, and the authors had at their disposal and the clarity of the groupings according to the change in their renal function. Limitations relate to the fact that at the core, the collected data represent an unavoidably biased sample. Early-stage CKD is disproportionately represented. In most cases, only a minority of these would be expected to deteriorate to ESRD in the timescale allocated. Furthermore, people within the community do not undergo multiple creatinine assessments over a 12-month period for no reason. This does not necessarily detract from the validity of the results, but it should be remembered that it is a study of those people who, presumably for clinical purposes, required at least two creatinine measurements within the year.

The results are interesting, even beguiling, in that the same two retrospective eGFR appraisals essential to define group status proved unhelpful in predicting a further drop in function. This suggests that the risk of deterioration in renal function is more accurate if a single estimate of eGFR is used rather than two estimates in the previous 12 months. What does this mean for the clinician? It could be that the CKD stage at the time of the last assessment already captures the drop in renal...
function over a 12-month period, and reviewing data within the previous 12 months will be unhelpful or worse (in effect, that the current CKD stage is the more powerful predictor of ESRD). It could also be that subjects underwent a second creatinine measurement for specific reasons that are unable to be determined in such a study, but was possibly in response to the first test result. Furthermore, it is important to emphasize the retrospective nature of the study: it is not possible to state whether a prospective appraisal would provide the same results, and great caution must be exercised in predicting future events from retrospective analyses. It is also unknown whether additional measures of eGFR or examination of a longer retrospective period would have reinforced or hindered the consistency of the findings.

Two other points are worth making. First, patients whose eGFR did not change by >25% do appear to have a relatively good prognosis for the 3.5-year median follow-up at least, regardless of whether one or both eGFR assessments were used. This is reassuring to some extent, but may fail to identify patients whose renal function is declining slowly, and who arguably have most to gain by small but long-lasting treatment effects, such as blood pressure control. Second, subjects whose eGFR improved over the 12 months also showed an increased risk of ESRD when both samples were used. As suggested above, this is not an isolated finding [20, 21]. Although one can only speculate on the reasons, the dependence of creatinine on variables such as nutrition, volume status and muscle mass, lack of specificity with normal aging and other unmeasured risk factors such as blood pressure, medication and resolving acute kidney injury are likely to be relevant. It is also noteworthy that the adverse variables most closely associated with each other were in the 'Certain drop' and 'Certain rise' groups. Juxtaposed with the relatively good outlook for those with stable measures, the very fact that the creatinine is labile may signify risk and alert clinicians when faced with an individual’s results. Proper, prospective studies will help address these questions further.

Like the profile of the disease itself, our capacity to detect and understand the presence and risk of progression of CKD is evolving. To address the global health risk to life and well-being, it is essential that current methods of detection are further refined and that the risk of progression continues to be elucidated. Studies which ascertain the effectiveness, both positive and negative, of clinical markers to identify the patients most at risk of deterioration are useful adjuncts in a long battle—as long as we remember that the rear-view mirror is not a substitute for the windscreen.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES


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