REVIEW ARTICLE

Laboratory Improvements in, and Importance of, Early Diagnosis of Chronic Kidney Disease

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Introduction:

Chronic kidney disease (CKD), a silent killer, is the progressive loss of renal function. As the disease progresses, CKD can cause complications, eg. cardiovascular disease, anaemia and bone disease, may drastically affect the quality of life, may lead to end-stage renal disease (ESRD) and may shorten life expectancy. Thus, detection and treatment of CKD at a far earlier stage may improve patient outcome and limit healthcare costs. Recently reported improvements in laboratory methodologies in, and importance of, early diagnosis of CKD are reviewed in the present article.

Chronic kidney disease (CKD) is the progressive loss of renal function. It can take many years before specific symptoms become evident. By that time quality of life may be drastically affected and life expectancy shortened. CKD is a silent killer and its incidence is increasing worldwide. Early diagnosis and treatment is vital in order to reduce the impact of this debilitating and potentially fatal condition[1]. However, appropriate use of existing laboratory tests, alongside newer markers for kidney function, help make detection of CKD far easier.

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Initial symptoms are unspecific and include a general feeling of being unwell. As the disease progresses, CKD can cause complications, eg. cardiovascular disease, anaemia and bone disease. Its most severe form may result in end-stage renal disease (ESRD)[1]. Patients with ESRD will require renal function replacement therapy through either regular dialysis or a kidney transplant. The number of patients with CKD is rising and that number is predicated to continue to rise by 5-8% annually[2]. Worldwide, approximately 1.8 million people already have ESRD[3]. The National Kidney Foundations (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI), UK guidelines divide (CKD) into five stages depending on glomerular filtration rate (GFR) (Table 1)[2,3].

Risk Factors for CKD :

Both diabetes and hypertension are major causes of CKD and are readily detectable and treatable. Close monitoring and control of these diseases may help to reduce the incidence and progression of CKD[4]. Glomerular nephritis, polycystic kidney disease, urinary tract infection, kidney stones, autoimmune disease and the toxic effects of some drugs also increase the risk of CKD. Because, like hypertension and diabetes, these conditions may damage the kidney. CKD is more likely to be seen in the elderly; its prevalence in adults over the age of 70 being 16% (11% in the general population) in the

Table I. Five stages of kidney disease

Stage	Description	GFR (mL/min/1.73m^2)
	At increased risk	>90(with CKD risk factors)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild or ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	12-29
5	Kidney failure	<15 (or dialysis)
Adapted from the 2002 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), UK clinical practice guidelines.		

UK[5]. Lower socioeconomic status and a family history of CKD also increase the risk[6,7,8].

Creatinine Testing and Significance of eGFR:

Clinical laboratory measurement of plasma creatinine concentration has been used to assess patient kidney function for well over 50 years. However, there must be considerable loss of function before plasma creatinine concentration begins to increase significantly and reliably above the upper limit of the reference range. This means that plasma creatinine is an ineffective marker during the early asymptomatic stages of CKD when GFR is the only reliable indicator.

In a normal kidney protein cannot pass through the semipermeable membrane of the glomerulus. However, as the nephron is progressively damaged in CKD, proteins of larger molecular weight are able to pass through and their presence can be found in the urine. A significantly reduced GFR and the presence of protein in the urine are indicators of declining kidney function. In the USA, the National kidney Disease Education Program (NKDEP),an initiative of the National Institutes of Health, defines CKD as the persistent and usually progressive reduction in (GFR) <60mL/min/1.73 m^2) and/or the presence of microalbuminuria (>30 mg urine albumin/g urine creatinine)[9,10].

Estimation of GFR requires accurate creatinine testing and the use of a predicative equation. The NKDEP Laboratory Working Group, in collaboration with the International Federation of Clinical Chemistry (IFCC) and

Table II: MDRD equation for use with IDMS-standardised creatinine results

The MDRD equation for use with IDMS-standardised creatinine results*
eGFR (mL/min/1.73m^2)=175x(serum creatinine, mg/dL)$^{-1.154}$ x(age)$^{-0.203}$ x 0.742 (if female) x 1.212 (if African-American)
* The MDRD equation for use with conventional creatinine results (not traceable to IDMS) is different only in the first term of the equation; For SI units (serum creatinine, μmol/L), divide the (serum creatinine, μmol/L) result by 88.4 to obtain mg/dL and use the equations above; As GFR varies with body size, it is common practice to correct for deviation from a standard adult body surface area of 1.73m^2, so height and weight (from which body surface area is calculated) must also be recorded.

the European Communities Confederation of Clinical Chemistry (ECCCC), recommends that creatinine assay methodologies be standardised to isotope dilution mass spectrometry (IDMS) and estimated GFR (eGFR) should be reported along with creatinine using the 'modification of diet in renal disease (MDRD)' equation (Table II)[11,12,13]. Alternatively, MDRD equations also exist that use creatinine μ mol/L results directly as stated in Table III[14,15].

Due to inter-laboratory differences in calibration of creatinine assays and the imprecision of the measurements at higher rates, the eGFR calculation has its greatest impact in the near-normal range. Therefore, the NKDEP recommends reporting eGFR values greater than or equal to 60 mL/min/1.73 m^2, simply as ≥60 mL/min/1.73/m^2 and not as an exact number. For values below 60 mL/min/1.73/m^2, creatinine values should be reported to the nearest whole number (for μ mol/L), and eGFR levels to the nearest whole number. Although an excellent tool for assessing kidney function, eGFR derived from the MDRD equation may not be suitable for all populations. The MDRD equation has been validated for adults aged between 18 and 70 years. The eGFR calculation using the MDRD equation is a more accurate measure of kidney function than is a creatinine clearance calculated from serum and urine measurements for most adults. Creatinine clearance is not recommended by the NKDEP, except in adults whose basal creatinine production is expected to be very abnormal[10]. In adults the best equation for eGFR from serum creatinine is the MDRD equation[14,15].

Other equations are used to estimate kidney function in more specific populations and circumstances. The Schwartz equation is used commonly for children under 18, and the Cockcroft-Gault equation is often used by pharmacies to estimate renal function when dosing drugs that depend on renal clearance rates. Clear communication and coordination between healthcare providers and laboratory staff is necessary when changing or standardising creatinine assays or when implementing GFR equations. Providers need to be notified about potential shifts in reported creatinine values following the implementation of serum creatinine methods with calibration traceable to IDMS. Furthermore, the Cockcroft-Gault, Schwartz

Table III: Estimating eGFR from plasma creatinine for staging CKD

eGFR (mL/min/1.73m^2)= 186 x (plasma creatinine [μ mol/L]x0.0113212)$^{-1.154}$ x (age[years])$^{-0.203}$ x (1.212 if African-American) x (0.742 if female)
This is the four-variable [body surface area, age, ethnicity and gender]) Modification of Diet in Renal Disease [MDRD] formula for estimating GFR from plasma creatinine concentration. The 1999 MDRD study allowed generation of the original six-variable formula from which this version is derived. This equation should be used only with those creatinine methods that have not been recalibrated to be traceable to IMDS. CKD may be stable or progressive. Progress is defined as decline in eGFR of >5mL/min/1.73m^2 in one year or >10 mL/min/1.73 m^2 in five years.

and Counahan-Barratt equations may give values that are higher than those obtained using traditionally calibrated creatinine methods[11,12,16].

Assay Parameters and Method:

Creatinine

The traditional methodology for measuring creatinine is the Jaffé method, also known as the alkaline picrate method. However, increasingly more expensive enzymatic methods are being used especially for specialised testing. It is important to point out that both the Jaffé and enzymatic methods are capable of being standardised to the same IDMS reference method and give similar recoveries. Both have different interferences, which means that each may be suited to different clinical scenarios and patient populations.

Considerable care should be taken when using the Jaffé method for neonatal samples and samples containing cephalosporins. In addition, some creatinine results can vary depending on the protein concentration of the sample. Interference from glucose and ketoacids can be a problem in diabetics[11]. For enzymatic creatinine assays based on the generation of hydrogen peroxide, dopamine and dobutamine interferences have been reported. Although enzymatic methods have improved, they still do not show complete specificity for creatinine[12]. Bilirubin has been shown to interfere with both assays[17].

Microalbumin

The term microalbumin (or urine albumin) is defined as the presence of low concentrations of albumin in urine. One of the first proteins seen in the urine of patients with early reduced kidney function is albumin. Routine assessment of microalbumin in patients with diabetes, hypertension or CKD is now recommended by NKDEP and NKF. To account for fluctuations in fluid balance and urine output, NKDEP recommends that laboratories should also report the ratio between urine albumin and urine creatinine, known as albumin-to-creatinine ration (ACR), when testing for urine albumin, and suggests reporting the ACR measurement in terms of mg/g. Pressure is also coming from nephrologists who are increasingly recognising the need to intervene earlier with patients who have risk factors and show signs of proteinuria. Their concern is reflected in the latest National Institute for Health and Clinical Excellence (NICE) guidelines, which indicate that using the ACR measurement under appropriate circumstances is the preferred approach for more accurate—and early—diagnosis of renal disease[8,13].

Cystatin C

Increasingly, cystatin C is being recognised as an additional or alternative marker to creatinine for renal function under certain circumstances[18]. It is reported to be dependent only on the GFR and has the advantage of not being affected by factors that can influence creatinine (eg diet, muscle mass or gender). This marker could therefore be useful for calculating eGFR in children, the elderly and adults with low muscle mass, perhaps because of diet or amputation[19]. In recent study, Schwartz updated his equation, which is used for estimating GFR in children, to include creatinine, urea, cystatin C, gender and height[20]. Cystatin C may also be useful for patients undergoing chemotherapy and other conditions where rapid detection of changes in

GFR is required. Cystatin C may be more sensitive to smaller initial declines in eGFR than is creatinine[21]. Research shows it may also have a role to play as a marker of cardiovascular risk[22]. Some diagnostic companies are now including this assay in their chemistry analyser menus to provide laboratories with a wider armoury in the early detection of CKD[16].

Importance of Regular Testing and Early Detection:

As the early symptoms of CKD are often silent and unspecific, many patients are identified only through screening. Therefore, the role of the clinical laboratory in the fight against this debilitating condition is crucial. It is therefore advisable for clinicians to screen regularly patients known to be at risk of kidney problems, specifically those with diabetes, hypertension, anaemia, a family history of CKD and the elderly. Delay in diagnosing CKD may lead to poor health outcomes, lower quality of life and higher healthcare costs through faster progression to ESRD. In contrast, prompt diagnosis enables co-morbidities (eg hypertension, poor glycaemic control in diabetes, smoking and poor diet) to be controlled, limiting further kidney damage and delaying ESRD[16].

Limitation of eGFR:

Despite its widespread adoption, however, eGFR is acknowledged as an imperfect test with limitation. A recently published cautionary case history highlights this aspect and demonstrates one way in which eGFR can lead to a false diagnosis of CKD. The case history demonstrates the wider point that the eGFR is only an estimate, and is least reliable in those with normal and near-normal GFR. When true (measured) GFR was 88 mL/min in the index patient, his eGFR was only 61 mL/min. The unreliability of eGFR when GFR is normal or close to normal is reflected in guidance that CKD should not be diagnosed on the basis of eGFR alone if eGFR is in the range 60-90 mL/min. Only if other evidence (eg. excess protein or blood in urine) is also present should the diagnosis be applied in such circumstances[23].

Recommendations:

The clinical laboratory has a vital role to play in the detection of CKD, due to the silent nature of the disease. Laboratories must ensure best practices are applied by adopting recommended guidelines and standards in order to gauge a patient's risk properly. These include:

- adopting NKDEP recommendations to reduce bias in serum creatinine measurement and yield more accurate GFR estimates.
- ensuring that creatinine assay methodologies are standardised to IDMS.
- selecting Jaffé and enzymatic assay methodology, depending on the likely interferents.
- reporting eGFR with creatinine using the MDRD equation, as appropriate.

Where the MDRD is not appropriate for assessing eGFR in some groups (eg children and the elderly), other equations and different methods should be used. The laboratory's use of other markers, including cystatin C, may help to improve estimation of GFR in these individuals. Increasingly, laboratory best practices highlight the provision of a range of creatinine assay methodologies (all standardised to IDMS) alongside additional

alternative assays such as cystatin C. This combined strategy is required to detect and treat CKD at a far earlier stage, thus improving patient outcome and limiting healthcare costs.

References:

1. Go AS, Chertow GM, Fan D, et al. Chronic Kidney disease and the risks of death, cardiovascular events and hospitalization. N Engl J Med 2004; 351: 1296-306.
2. Hamer RA, El Nahas AM. The burden of chronic kidney disease. BMJ 2006; 332: 563-64.
3. World Health Organization. Why should WHO be involved in transplantation? Department of Essential Health Technologies (www.who.int/eht/Transplantation.pdf) (Accessed on 29.08.2010).
4. NKF KDOQI. Guidelines for anemia of chronic kidney disease (www.kidney.org/professionals/kdoqi/guidelines_updates/doqiupan_i.html) (Accessed on 29.08.2010).
5. Coresh J, Astor BC, Greene T, et al. Prevalence of Chronic kidney disease and decreased kidney function in the adult US population: third national health and nutrition examination survey. Am J Kidney Dis 2003; 41: 1-12.
6. Mahon A. Managing CKD. EDTNA ERCA J 2006; 32: 70-72.
7. Levery AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification and stratification. Ann Int Med 2003; 139: 137-47.
8. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007; 298:2038-47.
9. World Kidney Day (www.worldkidneyday.org/) (Accessed on 29.08.2010).
10. NKDEP recommendations for laboratory professionals and for creatinine standardization (www.nkdep.nih.gov/labprofessionals) (Accessed on 29.08.2010).
11. Myers GL, Miller WG, Coresh J, et al. for the National Kidney Disease Education Program Laboratory Working Group. Recommendations for improving serum creatinine measurement: a report from the Laboratory working group of the national Kidney Disease Education Program. Clin Chem 2006; 52: 5-18.
12. Peake M, Whiting M. Measurement of serum creatinine-current status and future goals. Clin Biochem Rev-2006; 27: 173-84.
13. National Kidney Disease Education Program. (www.nkdep.nih.gov/resources/UACR_GFR_QuickReference_508.pdf) (Accessed on 29.08.2010).
14. National Kidney Disease Education Program www.nkdep.nih.gov/professionals.htm (Accessed on 29.08.2010).
15. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999 Mar 16;130(6): 461–70.
16. Zakowski JJ. Chronic Kidney disease: Improvements in early diagnosis. Biomedical Scientist (Official Gazette of the Institute of Biomedical Science, UK) 2009 July; 551-55.

17. Cobbaert CM, Baadenhuijsen H, Weykamp CW. Prime time for enzymatic creatinine methods in pediatrics. Clin Chem 2009; 55: 549-58.
18. Herget-Rosenthal S, Bokenkamp A, Hofmann W. How to estimate GFR-serum creatinine, serum cystatin C or equations? Clin Biochem 2007; 40: 153-61.
19. Filler G, Bookenkamp A, Hofmann W, et al. Cystain C as a marker of GFR-history, indications and future research. Clin Biochem 2005; 38(1): 1-8.
20. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009; 20:629-37.
21. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem 2002; 48: 699-707.
22. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: emerging markers of cardiovascular disease and stroke. (www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/risk/Documents/EmergingCV_RiskFactors09.pdf) (Accessed on 29.08.2010).
23. Higgins C. Plasma creatinine and estimated GFR: a cautionary case history. Biomedical scientist (Official Gazette of the Institute of Biomedical Science, UK) 2010 April; 240-43.