

Evaluation of Renal Function Guidelines

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1. Use of serum creatinine concentration to assess level of kidney function

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- Serum creatinine alone should not be used as a measure of kidney function as it is particularly insensitive for identifying chronic kidney disease (CKD) in its early-to-middle stages and in certain patient groups (e.g. small body size, females, elderly) when population-based decision points are used. (Level III evidence, multiple large cohort studies in community and institutional settings, clinically relevant outcomes, strong effects)
- For minor changes in renal function, changes in serum creatinine compared to the patient's previous results are the best available tool where assay precision and within-person biological variation can be used to determine the Critical Change at a desired certainty.
- The use of age- and gender-specific cut-points (upper limits of normal) of serum creatinine level or the reciprocal of serum creatinine concentration do not sufficiently improve the sensitivity and specificity of the serum creatinine measurement for CKD detection to obviate the need for additionally calculating or measuring glomerular filtration rate (GFR). (Level III evidence, multiple large cohort studies in community and institutional settings, clinically relevant outcomes, strong effects)
- In vitro diagnostic manufacturers and clinical laboratories should calibrate serum creatinine assays to give results equivalent to the international reference method (Isotope dilution mass spectrometry). Where assay non-specificity is significant (e.g. the effect of non-creatinine chromogens on the Jaffè reaction), the assay standardisation should correct for this effect in individuals with otherwise normal serum biochemistry. (Level III evidence, multiple

**large cohort studies in community and institutional settings,
clinically relevant outcomes, strong effects)**

Background

Chronic kidney disease is a major public health problem in Australia and throughout the world. Based on data from the Ausdiab study (Chadban et al 2003), it is estimated that over 1.7 million Australian adults have at least a moderately severe reduction in kidney function, defined as an estimated GFR less than 60 mL/min/1.73 m². This pernicious condition is often not associated with significant symptoms or urinary abnormalities and is unrecognised in 80%–90% of cases (Chadban et al 2003, McClellan et al 1997, John et al 2004). Chronic kidney disease progresses at a rate that requires approximately 1900 individuals each year in Australia to commence either dialysis or kidney transplantation (McDonald et al 2005). Furthermore, the presence of CKD is one of the most potent known risk factors for cardiovascular disease, such that individuals with CKD have a 10- to 20-fold greater risk of cardiac death than age- and sex-matched controls without CKD (Foley et al 1998, Weiner et al 2004). Early detection of CKD in the primary care setting is therefore critically important for facilitating the timely institution of therapies proven to slow or prevent kidney failure progression, enhance the appropriate assessment and modification of cardiovascular risk, and inform decisions regarding the prescription of drugs excreted by the kidneys (Akbari et al 2004, Johnson et al 2004).

The most commonly used measure of overall kidney function in clinical practice is serum creatinine concentration. Unfortunately, this measurement is affected by many factors other than the level of kidney function and varies markedly with age, gender and muscle mass. Moreover, there are significant calibration issues associated with the measurement of serum creatinine that lead to inter-laboratory variation of up to 34% (Coresh et al 2002, Miller et al 2005). Consequently, many guidelines, including the K/DOQI (K/DOQI 2002), British Renal Association (Joint Specialty Committee of the Royal College of Physicians of London and the British Renal Association 2005) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines (Levey et al 2005) have recommended that serum creatinine concentration alone should not be used to assess the level of kidney function.

The objective of this guideline is to review the evidence pertaining to the use of serum creatinine concentration to reliably detect CKD and prevent its sequelae.

Search strategy

Databases searched: Text words for creatinine were combined with MeSH terms and text words for renal function or kidney function. The search was carried out in Medline (1966 – 18 April 2005). The conference proceedings of the American Society of Nephrology from 1994–2004 were also searched for trials.

Date of searches: 18 April 2005.

What is the evidence?

No randomised controlled trials (RCTs) are available which address this issue.

There have been no RCTs comparing the effect of employing serum creatinine concentration versus other measures of kidney function on relevant clinical outcomes, such as detection or prevention of CKD, prevention of cardiovascular disease or reduction in medication-related adverse events.

The relationship between serum creatinine concentration and GFR is hyperbolic and is influenced by age, gender, muscle mass, ethnicity, dietary protein intake, certain medications (e.g. trimethoprim, cimetidine) and laboratory analytical methods (K/DOQI 2002, Young et al 1975, Levey et al 1988). Consequently, serum creatinine concentration is generally considered inadequate for detecting mild-to-moderate kidney failure, such that patients must lose up to 50% or more of their kidney function before the serum creatinine value rises above the upper limit of normal, depending on how close a patient's baseline serum creatinine is to the upper reference limit (K/DOQI 2002, Levey et al 1999, BRA 2005). The critical serum creatinine concentration range over which CKD patients are often misclassified as having normal renal function is in the general vicinity of 80–120 $\mu\text{mol/L}$ (Levey et al 1999).

Choosing appropriate serum creatinine cut-off points which account particularly for the influence of age and gender and which accurately identify patients with CKD has proven to be extraordinarily difficult.

The diagnosis of CKD is usually suspected when the serum creatinine concentration is greater than the upper limit of the reference range, defined as the 97.5th percentile established empirically in a large sample of population that is considered healthy. One study determined the normal range for serum creatinine concentration to be 63–112 $\mu\text{mol/L}$ in men and 53–102 $\mu\text{mol/L}$ in women, based on 18,000 serum creatinine determinations using the Jaffé reaction (Lauture et al 1973). These intervals compare well with the data reported by Mazzachi et al (2000) for an Australian population of blood donors. Nevertheless, the use of these empiric reference ranges is limited by the untested assumption that the reference population is healthy with no

evidence of CKD. Ethnic differences may play a role, since Sugita et al (1992) found distinctly lower reference intervals for a Japanese population (62–109 $\mu\text{mol/L}$ for males and 45–75 $\mu\text{mol/L}$ for females). The well known increase in serum creatinine with age (e.g. NHANES III) has rarely been included in reference interval studies, such as those indicated above. Thus, the value of decision points based on age-appropriate reference intervals has not been subject to assessment. Moreover, reference intervals may be altered depending on the type of creatinine assay performed. Finally, there have been no studies of the diagnostic value of these upper limits for the detection of CKD.

Iseki et al (1997) attempted to identify serum creatinine concentrations that were predictive of a significantly increased risk of end-stage kidney disease (ESKD) in a community-based mass screening health examination program of 107,192 Japanese subjects over 18 years of age (51,122 men, 56,070 women), conducted by the Okinawa General Health Maintenance Association between April 1983 and March 1984. Serum creatinine concentrations were ordered in the event of an abnormal urinalysis, hypertension, any other identified problems or upon patient request. The cumulative incidence of ESKD increased linearly with baseline serum creatinine level in both men and women, although the incidence of ESKD was higher in women than in men at every serum creatinine level. The adjusted relative risk of ESKD became significant at a serum creatinine level of 105 $\mu\text{mol/L}$ in women and 125 $\mu\text{mol/L}$ in men. For each 18 $\mu\text{mol/L}$ rise in serum creatinine concentration above these cut-off points, the risk of ESKD increased by 5.31 in men and 3.92 in women. However, the limitations of this study and its recommended cut-points include the limited generalisability of data from Japanese to Australian and New Zealand populations, and the possibility of selection bias, given that serum creatinine determinations were only performed in patients with observed risk factors for CKD (it should also be noted that the cumulative incidence of ESKD was 4 times higher in those who had a blood test in the 1983 mass screening compared with those who did not).

Couchoud and coworkers (1999) attempted to define cut-off values for serum creatinine as an indicator of several levels of kidney disease using data obtained from laboratory assessments of renal function (Jaffé reaction serum creatinine and inulin clearance measurements) in 984 patients (464 women, 520 men). The patients were recruited from various medical units and included individuals suspected of having CKD, those with risk factors for CKD and 83 'healthy' patients (healthy volunteers and living-related kidney donors). Using receiver operator curves constructed from the data and the Youden index ($[\text{sensitivity} + \text{specificity}] - 1$), which gives equal weighting to false positives and false negatives, the authors calculated that, for a measured GFR of 60 mL/min/1.73m², the cut-off values for serum creatinine concentrations were 137 $\mu\text{mol/L}$ for men and 104 $\mu\text{mol/L}$ for women. Cut-offs were similarly defined for measured GFR values of 80 mL/min/1.73 m² (115 and 90 $\mu\text{mol/L}$, respectively) and 30 mL/min/1.73 m² (177 and 146 $\mu\text{mol/L}$, respectively). The principal weakness of this study was ascertainment bias, in that patients without CKD were greatly under-represented. One cannot

therefore be sure of the diagnostic accuracy of these cut-offs in the primary healthcare setting.

Couchoud et al (1999) did attempt to address this limitation by determining projected predictive values for several plausible values of prevalence, assuming a sensitivity of 90%. For an estimated 10% prevalence of GFR < 60 mL/min/1.73 m² (i.e. similar to that reported by AusDiab), the positive predictive value for the cut-offs would only be approximately 60%, meaning that many healthy patients would be 'caught' by the screening study and possibly be subjected to unnecessary investigations and anxiety. It could also be argued that the use of cutpoints in serum creatinine that disregard age are biologically implausible and are likely to result in overestimation of kidney function in older people due to the confounding effect of age-related sarcopenia. Couchoud and coworkers reported that they had validated their cut-points in age-specific subgroups, but did not provide these data. The relatively small size of their population makes a type 2 statistical error likely.

Numerous general and patient population studies have demonstrated that measuring serum creatinine level is insensitive for detecting mild-to-moderate kidney failure, especially in the elderly and females.

The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study (Chadban et al 2003) was a national population-based cross-sectional survey of indicators of kidney damage in 11,247 non-institutionalised Australians aged 25 years or over, randomly selected using a stratified, cluster method. A representative sample of the national population was drawn from 42 randomly selected urban and nonurban areas (census collector districts) across Australia, with six census-collector districts in each of the six states and the Northern Territory. An elevated serum creatinine level was found in only 1.06% of the cohort, indicating that the upper reference limit was set higher than standard protocols dictate. However, the prevalence of CKD, defined as a Cockcroft-Gault eGFR less than 60 mL/min/1.73 m², was 11.2%. The prevalence of an estimated GFR < 30 mL/min/1.73 m² was 0.3%. Subsequent analyses using either Cockcroft-Gault or MDRD eGFRs have shown that, in patients with normal serum creatinine concentrations (< 120 µmol/L), the prevalence of an eGFR < 60 mL/min/1.73 m² is relatively high over the age of 65 years (Table 1).

The principal limitation of the AusDiab study is that the presence of CKD was defined according to estimated, rather than measured, GFR, such that significant misclassification of CKD by estimated GFR could not be excluded. The precision and accuracy of eGFR compared with measured GFR is discussed in detail in a following guideline ('Use of estimated GFR to assess level of kidney function'). The other limitations of the AusDiab study were the lack of partitioning of data for age and sex, which may have dramatically affected the results of the study if they had been used. For example, the upper reference interval of 120 µmol/L was clearly invalid as only 1.06% of the entire population was outside this limit, when strictly this should have been 2.5%. Moreover, the assay in use for the studies may have had a significant effect,

even if a good reference interval had been established for a particular method, since the use of non-method adjusted GFR estimates (MDRD or Cockcroft-Gault) could have introduced study biases.

Clase et al (2002) examined the prevalence of CKD in 13,251 adult, non-diabetic black and white Americans sampled in the Third National Health and Nutrition Examination Survey (NHANES III), using Couchoud creatinine cut-points, reciprocal creatinine, Cockcroft-Gault GFR and MDRD GFR. Compared with the two eGFR methods, Couchoud categories and reciprocal creatinine seriously underestimated the presence of CKD categories (GFR < 80, < 60 and < 30 mL/min/1.73 m²), particularly in those over the age of 60 years (i.e. the population at greatest risk of CKD).

Duncan et al (2001) studied 2781 outpatients referred by community physicians to an urban laboratory network in British Columbia, Canada, for serum creatinine measurement. Of the patients referred, 2543 (91.4%) had normal serum creatinine levels ($\leq 130 \mu\text{mol/L}$). Three hundred and eighty-seven (15.2%) of these 2543 patients with normal serum creatinine levels had Cockcroft-Gault GFRs $\leq 50 \text{ mL/min}$, representing substantially impaired renal function. The underdiagnosis of serious renal dysfunction increased with increasing age (1.2% 40–59 years old, 12.6% 60–69 years old, 47.3% over the age of 70 years). The limitations of this study were the lack of a ‘gold standard’ measure of GFR and the inability to differentiate transient renal dysfunction from early CKD. The authors attempted to address the latter issue by analysing available historical laboratory data. In each of the previous 4 years, 10%–20% of people who developed overt renal dysfunction had normal serum creatinine levels but Cockcroft-Gault GFR values $\leq 50 \text{ mL/min}$. This represented over half of the patients with normal serum creatinine and impaired eGFR at these time points, suggesting that a substantial number of patients with overt kidney failure pass through a stage of normal serum creatinine and impaired eGFR.

This situation of a ‘normal’ creatinine masking a significant decline in kidney function is especially important in elderly patients, in whom the age-related decline in kidney function may not be reflected by an increase in serum creatinine level because of a concomitant decrease in muscle mass.

Swedko and others (2003) conducted a retrospective medical record review of 865 patients aged 65 years and older in an outpatient academic family medicine practice in Canada. Significant kidney failure, defined as a Cockcroft-Gault GFR $\leq 50 \text{ mL/min}$, was found in 247 (28.9%) patients and severe kidney failure (Cockcroft-Gault GFR $\leq 30 \text{ mL/min}$) was present in 6.4%. As a test for kidney failure (Cockcroft-Gault GFR $\leq 50 \text{ mL/min}$) in the elderly, a serum creatinine measurement $> 150 \mu\text{mol/L}$ had a sensitivity of 12.6%, a specificity of 99.9%, and a negative likelihood ratio of 0.87, and was inconsistent across genders. The corresponding values for severe kidney failure (Cockcroft-Gault GFR $\leq 30 \text{ mL/min}$) were sensitivity 45.5%, specificity 99.1%, and negative likelihood ratio 0.55. Only 27.3% of patients with severe

kidney failure were referred to a nephrologist; the odds of being referred increased by 2.4 for each 20 $\mu\text{mol/L}$ increase in serum creatinine level above 150 $\mu\text{mol/L}$.

Cumming et al (2004) undertook a population-based, cross-sectional study of 3222 people aged ≥ 49 years (mean age: 65 years) in the general community in an urban area of the Blue Mountains, Australia. The study population represented 82% of the eligible community population. The proportion of patients with a serum creatinine level $\geq 125 \mu\text{mol/L}$ (13.5% of men and 4% of women) was much lower than the proportion with significant kidney failure (Cockcroft-Gault GFR $\leq 50 \text{ mL/min}$; 19% of men and 35% of women). Cockcroft-Gault GFR was strongly associated with the prevalence of anaemia, such that the attributable risk of CKD to anaemia was 68% in men and 82% in women. The major limitation of this study was the lack of a direct measure of GFR and the fact the Cockcroft-Gault GFR was not adjusted for body surface area.

In addition to predicting those at risk of progressing to ESKD, another key rationale for assessing kidney function level is to try to accurately identify and manage those individuals who are at increased risk of cardiovascular disease.

There are numerous reports that serum creatinine is associated with cardiovascular mortality (Wannamethee et al 1997, Ruilope et al 2001, Mann et al 2001, Langford et al 1986, Drey et al 2003, Shlipak et al 2001, Shlipak et al 2002, Muntner et al 2002, Shulman et al 1989). However, other investigators have not been able to identify an association between cardiovascular mortality and serum creatinine (Culleton et al 1999, Garg et al 2002).

A recent paper by Shlipak et al (2005) compared serum creatinine, estimated GFR (eGFR; calculated according to the abbreviated MDRD formula) and serum cystatin C as predictors of cardiovascular mortality in 4637 individuals aged 65 years or more who participated in the Cardiovascular Health Study. Unadjusted hazard ratios for cardiovascular death were significantly different from the reference group for the lowest 40% of eGFR values ($< 66.62 \text{ mL/min/1.73 m}^2$), but only the highest 14% of serum creatinine values ($>120 \mu\text{mol/L}$). Following multivariate adjustment for demographic factors and comorbid illnesses, the adjusted hazard ratios for death from cardiovascular causes were not significantly different between the lowest quintile (reference) and all other quintiles of serum creatinine. However, eGFR remained significantly and independently predictive of cardiovascular death in the patients with the lowest 7% of eGFR values ($< 45.64 \text{ mL/min/1.73 m}^2$). Hence, eGFR was more strongly predictive of cardiovascular death than serum creatinine. Interestingly, higher cystatin C levels were directly and dose-dependently associated with higher risks of all-cause and cardiovascular mortality and were more strongly predictive of these outcomes than either serum creatinine or eGFR. The limitations of this study were the possibility of residual confounding (especially as adjusted and unadjusted hazard ratios

varied substantially from each other) and the restriction of study participants to those aged 65 years and over (hence, it is uncertain whether similar mortality associations would be observed in younger populations).

Sources of error/bias in serum creatinine results

a) Errors in laboratory measurement

The traditional assay for measurement of creatinine is the alkaline picrate method (Jaffé reaction). There are now many variations of this method in use which produce results that overestimate serum creatinine levels by up to 27 $\mu\text{mol/L}$ for results in the reference interval, due to the presence of interfering, pseudochromogenic constituents, mainly proteins, in the blood (Wuyts et al 2003, Appel et al 2003, Van Lente et al 1989). Modern versions of Jaffe assays have minimised these effects by adjusting temperature, assay constituents, read frame, calibrator set points and offsets. Alternatively, the protein error can be reduced by the use of enzymatic creatinine methods (Wuyts et al 2003), HPLC or isotope dilution mass spectroscopy (Coresh et al 2002, Coresh et al 1998, Perrone et al 1992).

Calibration of serum creatinine measurements is not standardised, thereby leading to substantial variation within and between laboratories. Of 11 common biochemical tests evaluated across 700 laboratories by the College of American Pathologists, differences in calibration of serum creatinine assays (approximately 18 $\mu\text{mol/L}$ between labs) accounted for 85% of the difference between laboratories and were greater than for any of the other 10 analytes examined (Ross et al 1998). Serum creatinine concentration was over-estimated by an average of 13.3% compared with a reference method. Calibration biases appear to be particularly important at lower serum creatinine levels. In contrast, within-laboratory variation of serum creatinine was only 8%. Similar results were found among the 102 laboratories participating in the Nordic Reference Interval Project (NORIP) (Rustad 2003). A more recent evaluation of participants in the College of American Pathologists Chemistry Survey demonstrated that the mean bias for 50 instrument-method peer groups varied from -0.06 to 0.31 mg/dL (-5.3 to 27.4 $\mu\text{mol/L}$), with 30 (60%) of 50 peer groups having significant bias ($p < 0.001$) (Miller et al 2005).

b) Random errors

- The first source of variation in results is random error of the assay itself.
- The coefficient of variation for this error varies with the absolute serum creatine concentration and the laboratory methodology employed and has been reported to range from 1% (Hse et al 2002) to 11% (Perrone et al 1992). The median within-instrument precision for serum creatinine in the RCPA/AACB QAP is 3.5% (General Chemistry Program, End of Cycle report, Cycle 68, 2005).

c) Real short-term fluctuations in serum creatinine

- Serum creatinine concentration can vary significantly during the day and between consecutive days due to short-term variations in renal function (e.g. due to changes in hydration or posture), tubular creatinine secretion, extra-renal creatinine excretion and creatinine generation. Taken together, these effects give an average variation due to changes in the patient of a coefficient of variation of about 4.3% (www.westgard.com) although a value of 6.3% was recently obtained from NHANES III.

- Short-term variations in renal function
 - i. Perrone et al (1990) re-measured GFR in the same individuals within 7 to 28 days and showed that the between-day coefficient of variation in measured GFR ranged from 12%–17%.

- Variations in tubular creatinine secretion
 - i. In addition to being freely filtered by the glomerulus, creatinine is also secreted by the cation exchanger in the S2 segment of the proximal tubule.
 - ii. The proportion of total creatinine excretion by secretion, as opposed to glomerular filtration, ranges between 10% and 50% (K/DOQI 2002), Berlyne et al 1964). Variation in tubular creatinine secretion alters the relationship between serum creatinine level and GFR.
 - iii. Tubular creatinine secretion is inhibited by a number of medications competing for secretion by the proximal tubular cation exchanger, including cimetidine, trimethoprim, amiloride, procainamide, quinine, quinidine and cis-platinum (K/DOQI 2002, Young et al 1975). This can lead to a significant (up to 50%) elevation of serum creatinine concentration without a change in GFR.
 - iv. The proportion of creatinine secreted versus filtered into the urine rises as GFR falls, leading to a tendency for creatinine to underestimate GFR.

- Variations in extra-renal creatinine excretion
 - i. Extra-renal (via the gut) creatinine excretion is minimal in most people, but is increased in situations characterised by bacterial overgrowth of the small bowel.
 - ii. Small bowel bacterial overgrowth is common in CKD patients, such that two-thirds of total daily creatinine excretion can occur by extra-renal elimination in patients with severely reduced kidney function (Dunn et al 1997). The net effect is a tendency for serum creatinine to underestimate GFR.

- Variations in creatinine generation

- i. Creatinine is mainly derived from the metabolism of creatinine in muscle. Creatinine generation therefore tends to be proportional to muscle mass and is consequently influenced by age, gender, race, body size, nutritional status, catabolic status and the presence of certain disease states (e.g. muscle disorders, paraplegia, amputation) (Mitch et al 1980).
- ii. Creatinine generation is also affected by dietary meat intake, because the process of cooking meat converts a variable proportion of creatine to creatinine. Several authors have observed diurnal variation in serum creatinine concentrations of up to 30%, with the peak around 1900h, which has been attributed to dietary intake (Rappoport et al 1968, Pasternack and Kuhlback 1971).

d) Total measurement error for a single sample

- The variation on a single result for serum creatinine (CV_{tot}) can be calculated from the analytical coefficient of variation (CV_a) and the within-person biological variation (CV_{wi}) as follows:
$$CV_{tot} = \text{SQRT}(CV_a^2 + CV_{wi}^2)$$
- The critical difference, i.e. the smallest change that can be considered statistically significant can be estimated from this parameter. For example, a change of 2.77 times the CV_{tot} is required for 95% certainty when the change may occur in either direction.

Summary of the evidence

There are no RCTs on this topic. There have been no RCTs comparing the effect of employing serum creatinine concentration versus other measures of kidney function on relevant clinical outcomes, such as detection or prevention of CKD, prevention of cardiovascular disease or reduction in medication-related adverse events. Serum creatinine is affected by many factors other than the level of GFR, including laboratory calibration bias (of the order of 18 µmol/L), age, gender, race, body size, diet, certain drugs and some disease states. Consequently, no serum creatinine cut-off points have been developed to date, which effectively identify patients with CKD with acceptable sensitivity and specificity. The use of serum creatinine alone as a measure of kidney function is particularly insensitive at identifying CKD in its early stages and in certain patient groups (i.e. small body size, females, the elderly).

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: The serum creatinine concentration alone should not be used to assess the level of kidney function.

Autoanalyzer manufacturers and clinical laboratories should calibrate creatinine assays using an international standard.

British Renal Association: Within a renal network, which may or may not be co-terminous with a pathology network, laboratories should provide comparable creatinine results, ideally by use of identical methodology. This should be audited by internal quality control procedures across the network and satisfactory performance in a national quality assessment scheme. Renal/pathology networks should agree a common approach to the estimation of GFR.

Kidney function in patients with CKD should be assessed by formula-based estimation of GFR using either the 4-variable Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations (Level of evidence 3 DA).

Canadian Society of Nephrology: Use of serum creatinine as the only indicator of renal failure will fail to diagnose an abnormally low creatinine clearance in 35% of those 40 to 49 yrs old, and this increases to 92% of those > 70 yrs old.

European Best Practice Guidelines: Renal function should not be estimated from measurements of blood urea or creatinine alone. Dialysis terms such as Kt/V and weekly creatinine clearance should be avoided to reduce confusion when communicating with general physicians and to encourage timely referral of patients with renal failure.

International Guidelines: Kidney Disease Improving Global Outcomes: Serum creatinine measurements should be standardised.

Calibration should be traceable to a reference creatinine method (isotope dilution mass spectrometry).

Implementation and audit

Serum creatinine and eGFR at commencement of renal replacement therapy should be collected by the ANZDATA Registry.

Suggestions for future research

1. The usefulness of serum cystatin C measurement for determining level of kidney function (alone or in combination with creatinine) should be evaluated.

2. The effects of improved standardisation and reduced assay imprecision on early detection of changes in renal function should be evaluated.
3. The relative abilities of serum creatinine, eGFR and other measures of kidney function (e.g. serum cystatin C) to predict cardiovascular events and kidney disease progression should be evaluated and compared in population-based studies over a broad age range.

References

- Akbari A, Swedko PJ, Clark HD et al. Detection of chronic kidney disease with laboratory reporting of estimated glomerular filtration rate and an educational program. *Arch Intern Med* 2004; 164: 1788–92.
- Appel LJ, Champagne CM, Harsha DW et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 2003; 289: 2083–93.
- Berlyne GM, Varley H, Nilwarangkur S et al. Endogenous creatinine clearance and glomerular filtration rate. *Lancet* 1964; 22: 874–76.
- Chadban SJ, Briganti EM, Kerr PG et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 2003; 14(7 Suppl 2): S131–S138.
- Clase CM, Garg AX, Kiberd BA. Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 2002; 13: 1338–49.
- Coresh J, Astor BC, McQuillan G et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002; 39: 920–29.
- Coresh J, Toto RD, Kirk KA et al. Creatinine clearance as a measure of GFR in screenees for the African-American Study of Kidney Disease and Hypertension pilot study. *Am J Kidney Dis* 1998; 32: 32–42.
- Couchoud C, Pozet N, Labeeuw M et al. Screening early renal failure: cut-off values for serum creatinine as an indicator of renal impairment. *Kidney Int* 1999; 55: 1878–84.
- Culleton BF, Larson MG, Wilson PW et al. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999; 56: 2214–19.
- Cumming RG, Mitchell P, Craig JC et al. Renal impairment and anaemia in a population-based study of older people. *Intern Med J* 2004; 34: 20–23.
- Drey N, Roderick P, Mullee M et al. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* 2003; 42: 677–84.
- Duncan L, Heathcote J, Djurdjev O et al. Screening for renal disease using serum creatinine: who are we missing? *Nephrol Dial Transplant* 2001; 16: 1042–46.

Dunn SR, Gabuzda GM, Superdock KR et al. Induction of creatininase activity in chronic renal failure: timing of creatinine degradation and effect of antibiotics. *Am J Kidney Dis* 1997; 29: 72–77.

Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32(5 Suppl 3): S112–S119.

Garg AX, Clark WF, Haynes RB et al. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int* 2002; 61: 1486–94.

Hsu CY, Chertow GM, Curhan GC. Methodological issues in studying the epidemiology of mild to moderate chronic renal insufficiency. *Kidney Int* 2002; 61: 1567–76.

Iseki K, Ikemiya Y, Fukiyama K. Risk factors of end-stage renal disease and serum creatinine in a community-based mass screening. *Kidney Int* 1997; 51: 850–54.

John R, Webb M, Young A et al. Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis* 2004; 43: 825–35.

Johnson CA, Levey AS, Coresh J et al. Clinical practice guidelines for chronic kidney disease in adults: Part I. Definition, disease stages, evaluation, treatment, and risk factors. *Am Fam Physician* 2004; 70: 869–76.

Joint Specialty Committee of the Royal College of Physicians of London and the British Renal Association. *Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral*. London; 2005. Available from: <http://www.renal.org/CKDguide/full/UKCKDfull.pdf>

Langford HG, Stamler J, Wassertheil-Smoller S et al. All-cause mortality in the Hypertension Detection and Follow-up Program: findings for the whole cohort and for persons with less severe hypertension, with and without other traits related to risk of mortality. *Prog Cardiovasc Dis* 1986; 29(3 Suppl 1): S29–S54.

Lauture de H, Caces E, Dubost P. Concentrations of cholesterol, uric acid, urea, glucose and creatinine in a population of 50,000 active individuals. In: Siest G, editor. *Reference values in human chemistry*. Basel: Karger; 1973. p. 141–52.

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; 130: 461–70.

Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. *Annu Rev Med* 1988; 39: 465–90.

Levey AS, Eckardt KU, Tsukamoto Y et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67: 2089–100.

Mann JF, Gerstein HC, Pogue J et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; 134: 629–36.

Mazzachi BC, Peake MJ, Ehrhardt V. Reference range and method comparison studies for enzymatic and Jaffe creatinine assays in plasma and serum and early morning urine. *Clin Lab* 2000; 46: 53–55.

McClellan WM, Knight DF, Karp H et al. Early detection and treatment of renal disease in hospitalized diabetic and hypertensive patients: important differences between practice and published guidelines. *Am J Kidney Dis* 1997; 29: 368–75.

McDonald S, Russ G. New patients commencing renal replacement therapy in 2003. In: McDonald S, Russ G, editors. ANZDATA Registry Report 2003. Adelaide, SA: Australian and New Zealand Dialysis and Transplant Registry, 2005: 8–15.

Miller WG, Myers GL, Ashwood ER et al. Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. *Arch Pathol Lab Med* 2005; 129: 297–304.

Mitch WE, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. *Clin Sci (Lond)* 1980; 58: 327–35.

Muntner P, He J, Hamm L et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 2002; 13: 745–53.

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 2002; 39(Suppl 1): S1–266.

Pasternack A, Kuhlback B. Diurnal variations of serum and urine creatine and creatinine. *Scand J Clin Lab Invest* 1971; 27: 1–7.

Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; 38: 1933–53.

Perrone RD, Steinman TI, Beck GJ et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of ¹²⁵I-iothalamate, ¹⁶⁹Yb-DTPA, ^{99m}Tc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 1990; 16: 224–35.

Polkinghorne KR, Chadban SJ, Shaw JE et al. Prevalence of impaired GFR in Australia: a comparison between the Cockcroft-Gault and Modification of Diet in Renal Disease equations. *Nephrology* 2005; 10(Suppl). In press.

Rapoport A, Husdan H. Endogenous creatinine clearance and serum creatinine in the clinical assessment of kidney function. *Can Med Assoc J* 1968; 99: 149–56.

Ross JW, Miller WG, Myers GL et al. The accuracy of laboratory measurements in clinical chemistry: a study of 11 routine chemistry analytes in the College of American Pathologists Chemistry Survey with fresh frozen serum, definitive methods, and reference methods. *Arch Pathol Lab Med* 1998; 122: 587–608.

Ruilope LM, Salvetti A, Jamerson K et al. Renal function and intensive lowering of blood pressure in hypertensive participants of the Hypertension Optimal Treatment (HOT) Study. *J Am Soc Nephrol* 2001; 12: 218–25.

Rustad P. Reference intervals for 25 of the most frequently used properties in clinical chemistry: proposal by the NORDIC Reference Interval Project (NORIP). *Klinisk Biokemi I Norden* 2003; 15: 10–17.

Shlipak MG, Simon JA, Grady D et al. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol* 2001; 38: 705–11.

Shlipak MG, Heidenreich PA, Noguchi H et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002; 137: 555–62.

Shlipak MG, Sarnak MJ, Katz R et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005; 352: 2049–60.

Shulman NB, Ford CE, Hall WD et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the Hypertension Detection and Follow-up Program. *Hypertension* 1989; 13: 180–93.

Sugita O, Uchiyama K, Yamada T et al. Reference values of serum and urine creatinine, and of creatinine clearance by a new enzymatic method. *Ann Clin Biochem* 1992; 29(Pt 5): 523–28.

Swedko PJ, Clark HD, Paramsothy K et al. Serum creatinine is an inadequate screening test for renal failure in elderly patients. *Arch Intern Med* 2003; 163: 356–60.

Van Lente F, Suit P. Assessment of renal function by serum creatinine and creatinine clearance: glomerular filtration rate estimated by four procedures. *Clin Chem* 1989; 35: 2326–30.

Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke* 1997; 28: 557–63.

Weiner DE, Tighiouart H, Amin MG et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004; 15: 1307–15.

Wuyts B, Bernard D, Van den NN et al. Reevaluation of formulas for predicting creatinine clearance in adults and children, using compensated creatinine methods. *Clin Chem* 2003; 49: 1011–14.

Young DS, Pestaner LC, Gibberman V. Effects of drugs on clinical laboratory tests. *Clin Chem* 1975; 21: ID–432D.

Appendix

Table 1 Prevalence of Cockcroft-Gault (C-G) or MDRD eGFR < 60 mL/min/1.73 m² in AusDiab Study subjects with normal serum creatinine concentration ($\leq 120 \mu\text{mol/L}$) according to age

eGFR	Prevalence of eGFR < 60 mL/min/1.73 m ² by age category (yr)					
	25–34	35–44	45–54	55–64	65–74	≥ 75
C-G	0%	0%	0.6%	4.8%	38.1%	77.4%
MDRD	0.3%	0.4%	3.9%	6.7%	23.0%	37.0%

Source: Polkinghorne et al 2005