Creatinine (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Creatinine

1.2 Alternative names
None

1.3 Description of analyte
Creatinine is a heterocyclic nitrogenous compound (IUPAC 2-amino-1-methyl-5H-imidazol-4-one), MW 113 Da. It is produced from creatine in muscle at a rate dependent on muscle bulk and is excreted unchanged by the kidneys, mainly by glomerular filtration but to a small extent by active secretion.

A small amount of creatinine (approximately 10%) is derived from dietary sources (particularly cooked meat).

1.4 Function of analyte
Creatinine is not known to have any physiological function: it is a waste product.

2 Sample requirements and precautions

2.1 Medium in which measmured
This article relates to the measurement of creatinine in serum; its measurement in urine may be useful in the assessment of renal function, and as a component of ratios with other analytes in the assessment of their excretion (e.g. calcium:creatinine ratio) to reduce the variation due to urinary concentration.

2.2 Precautions re sampling, handling etc.
No specific precautions are required.

3 Summary of clinical uses and limitations of measurements

3.1 Uses
1. Serum creatinine measurement is used as a test of renal function. It is superior in this respect to [urea], which is influenced considerably by non-renal factors including protein turnover (whether derived from the diet or endogenously) and the state of hydration.
2. Serum [creatinine] is used to monitor progression and treatment in acute kidney injury and chronic kidney disease (CKD). In acute kidney injury, the frequency of measurements will usually be guided by clinical factors and the need to monitor serum [potassium] but is unlikely to be less than once in 24 h.

In patients with CKD stages 1-3 (i.e. eGFR ≥60 mL/min) measurements should be made 6- or at least 12- monthly according to whether eGFR is changing by more or less than 15 mL/min, respectively, between successive measurements; in patients with more advanced CKD, the corresponding figures are 3- and 6-monthly.

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3. Serum [creatinine] can be combined with measurements of urine creatinine in timed urine specimens to generate the creatinine clearance, an indicator of the glomerular filtration rate (GFR). Such measurements have poor reproducibility owing to the imprecision imposed by the difficulty in collecting accurately timed urine specimens.
4. Serum [creatinine] can be used together with demographic information (e.g. age, race, sex) to calculate an estimated GFR (eGFR). In the UK, it is recommended that eGFR should be based on the MDRD (Modification of Diet in Renal Disease) 4-variable formula (e.g. Levey AS, Coresh J, Greene T *et al* for the Chronic Kidney Disease Epidemiology Collaboration. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. Ann Int Med 2006;145:247-254). However, this concept is open to criticism (e.g Giles PD, Fitzmaurice DA. Formula estimation of glomerular filtration rare: have we gone wrong? BMJ 2007;334:1198-2000) and is not applicable to several clinical situations e.g. acute kidney disease, children, individuals with muscle-wasting etc.

3.1 Limitations

Serum [creatinine] has a wide normal reference interval; it is inversely related to GFR. As a result, GFR may fall to half normal before serum [creatinine] exceeds the upper reference limit. The influence of muscle bulk and, to a much lesser extent, dietary protein intake, on creatinine production, means that a (slightly) elevated [creatinine] may not indicate impaired renal function

4 Analytical considerations

4.1 Analytical methods

1. Chemical

These methods are based on the Jaffé reaction, in which creatinine reacts with picrate in alkaline solution to form an orange-red complex with an absorption maximum at 490–500 nm, which is measured spectrophotometrically.

The major drawback of these methods are their lack of specificity: interfering substances include ketones, some drugs, e.g. cephalosporins (positive) and bilirubin (negative). This effectively negates the use of end-point assays.

The effects of interference have been successfully reduced by the adoption of kinetic assays, in which colour generation is typically measured between 20 and 80 seconds after initiation of the reaction (interfering substances tend to have an immediate (<20 sec. e.g. ketones) or later effect (>80 sec, e.g. protein), and reaction conditions, and reagent concentrations are precisely controlled. Such methods are widely used in automated analysers.

2. Enzymatic

a. Creatininase (creatinine aminohydrolase, EC 3.5.2.10) catalyses the conversion of creatinine to creatine. The latter can be measured through either (1) a reaction catalysed by creatinase (creatine aminohydrolase, EC 3.5.3.3) to urea and sarcosine, followed by enzymic measurement of the sarcosine using sarcosine oxidase (EC 1.5.3.1) to generate hydrogen peroxide, which is used to oxidise an indicator, or (2) a series of reactions catalysed by creatine kinase (EC 2.7.3.2), converting ATP to ADP; pyruvate kinase (EC 2.7.1.40) (phosphoenolpyruvate and ADP to

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pyruvate and ATP), and L-lactate dehydrogenase (EC 1.1.1.27) (pyruvate and NADH to lactate and NAD). Various techniques have been devised to reduce interference e.g. by endogenous creatine. Method (1) has been adapted for point-of-care use employing polarographic detection.
b. Creatinine deaminase (creatinine iminohydrolase EC 3.5.4.21) catalyses the conversion of creatinine to N-methylhydantoin and ammonia and provides the basis for another enzymatic method.
Both enzymes have been used as the basis for dry-slide methods to measure creatinine.
3. Isotope-dilution mass spectrometry (ID-MS)
This technique is potentially the definitive method, although not suitable for high-throughput use.

4.2 Reference method
A candidate reference method is based on isocratic HPLC.

4.3 Reference material
SRM (Standard Reference Material) 967; National Institute for Standards and Technology, Washington DC, USA.

4.3 Interfering substances
See discussion of individual methods.

4.4 Sources of error.
In order to reduce error, and maximise the comparability of [creatinine] measurements (and hence eGFR), most methods are now calibrated against ID-MS. This has made unnecessary the previous practice recommended by UKNEQAS that correction factors should be applied to results obtained by routine methods to relate them to ID-MS.

5 Reference intervals and variance

5.1.1 Reference interval (adults): typically 60-120 μmol/L (males), 55-100 μmol/L (females) using Jaffé-based methods
5.1.2 Reference intervals: the lower reference limit is lower in children, and varies with body mass.
5.1.3 Extent of variation
5.1.3.1 Interindividual CV: 10%
5.1.3.2 Intraindividual CV: 4.6%
5.1.3.3 Index of individuality: 45%
5.1.3.4 CV of method: 6.3%
5.1.3.5 Critical difference: 22%
5.1.4 Approximately up to 10% of total difference may be accounted for by diet. It should be noted that although the reference intervals for creatinine are wide, the intra-individual variation is relatively low.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation
1. Creatinine should be measured in patients suspected of having, or at risk of, impaired renal function, e.g because of shock, dehydration, exposure to potentially nephrotoxic drugs, clinical evidence of intrinsic renal disease.

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2. Creatinine should be measured in patients with known renal disease, to monitor the natural history or the response to treatment.

6.2 Confounding factors

The wide reference interval for [creatinine] and its being inversely correlated to glomerular filtration rate (GFR) results in its being an insensitive test for detecting early or relatively mild renal impairment. It is not useful as a screening test for early renal impairment e.g. in patients with diabetes, for which the detection of microalbuminuria is the recommended investigation.

7 Causes of abnormal results

7.1 High values.

7.1.1 Causes

The major causes are:

- renal impairment (acute and chronic)
- high muscle mass.

7.1.2 Investigation

In suspected renal impairment, investigation should be directed to determine the cause so that this can be treated if possible, in addition to providing renal replacement treatment if indicated. The cause of acute kidney injury is often clinically obvious. In CKD, it may not: numerous biochemical and other investigations may be of value; effective treatment of the underlying cause may slow or arrest the progression of the condition, but does not reverse it. Pointers to chronicity, when this is not apparent clinically, include the demonstration of small kidneys using imaging, the presence of anaemia and the presence of bone disease.
Both acute kidney injury and chronic kidney disease can cause hyperkalaemia, which can be fatal. Serum [potassium] should always be measured when serum [creatinine] is found to be raised.

7.2 Low values

7.2.1 Causes

The major causes are:

- over-hydration
- low muscle mass.

7.2.2 Investigation

The cause of a low [creatinine] is invariably clinically obvious, and specific investigations are not required.

7.3 Notes

Urea is often measured at the same time as creatinine. It is inferior to [creatinine] as an indicator of renal function, being considerably influenced by the rate of nitrogen turnover. In dehydration leading to pre-renal failure, however, plasma [urea] typically increases before [creatinine].

8 Performance

9

8.1 Sensitivity, specificity etc. for individual conditions

For the reasons discussed above, serum [creatinine] has low sensitivity (particularly) and specificity for the diagnosis of renal failure. However,

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the stages of chronic kidney injury are now defined by the eGFR (together with the presence of proteinuria), which is calculated from serum [creatinine] (see 3.1 (3)

9 Systematic reviews and guidelines

9.1 Systematic reviews

1. Coca SG, Peixoto AJ, Garg AX *et al*. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. Am J Kidney Dis. 2007;50:712-720. *Increases in serum [creatinine] of as little as 10–24% were associated with poor outcomes in a variety of hospital settings; the greatest increases were associated with the worst prognosis.*
2. Numerous other systematic reviews relate circumstances in which [creatinine] is used as an index of renal function in relation to the prevention or management of specific conditions.

9.2 Guidelines

1. National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, September 2008.
This guideline provides critical discussion of the role of serum [creatinine] and eGFR in the diagnosis and assessment of CKD.
2. UKeCKD Guide (revised 2009)
www.renal.org/whatwedo/InformationResources/CKDeGuide/Referral.aspx (accessed 25.iv.2012)
(*This guideline, based on the NICE, SIGN and Renal Association Guidelines, indicates when patients with chronic kidney disease should be referred to a nephrology service*.)

9.3 Recommendations

1. The recommendation that serum [creatinine] should be used to calculate eGFR is referred to in 3.1 (3).
2. Recommendations for referral of patients with chronic kidney disease based on serum [creatinine] have been superseded by guidelines based on eGFR (see 9.2).

10 Links

10.1 Related analytes

None

10.2 Related tests

Serum [urea] (see 7.3); serum [cystatin] also reflects renal function, but has not been shown to have any definite advantage over measurement of creatinine and calculation of eGFR.

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