

Cystatin C (serum, plasma, urine)

1 Name and description of analyte

- 1.1 Name of analyte
Cystatin C (serum, plasma and urine)
- 1.2 Alternative names
Cystatin 3, post-gamma-globulin, neuroendocrine basic polypeptide, gamma trace.
- 1.3 This number is not used
- 1.4. Function(s) of analyte
Cystatin C is an endogenous 13 kDa protein synthesised by all nucleated cells; its role is that of a cysteine protease inhibitor. Cysteine proteases degrade proteins and play a role in apoptosis, immune responses, remodelling of the extracellular matrix and prohormone processing.

Cystatin C is relatively freely filtered by the glomeruli owing to its relatively small size and high isoelectric point; it is reabsorbed and catabolised by proximal renal tubular cells. It is produced at a constant rate and plasma concentrations appear to be relatively unaffected by muscle mass, diet or gender.

2 Sample requirements and precautions

- 2.1 Medium in which measured
Cystatin C can be measured in plasma, serum and urine. Measurements in serum and plasma are generally equivalent.
- 2.2 Precautions re sampling, handling etc.
Serum can be collected into tubes with or without gel barriers. Complete clot formation should be ensured prior to separation, especially in patients on anticoagulant or thrombolytic therapy as there is a risk of formation of fibrin clots that could cause erroneous test results. Acceptable anticoagulants for plasma samples are lithium heparin, EDTA and sodium heparin. Random urine samples can also be analysed.

3 Summary of clinical uses and limitations of measurements

- 3.1 Uses
Serum and plasma cystatin C measurements are used as a surrogate marker of renal glomerular function, mainly in the detection of chronic kidney disease (CKD). Since it is freely filtered by the glomeruli and there is neither known extra-renal elimination nor tubular secretion, the concentration in the blood inversely correlates with the glomerular filtration rate (GFR). With the development of estimated glomerular filtration rate (eGFR) as the primary tool for assessment of renal function, GFR estimating equations have been developed that incorporate cystatin C for both adults (e.g. CKD-EPI_{cystatin C}) and children (e.g. CKiD). Equations based on cystatin C are potentially more accurate and reliable for detection of

mild to moderate impairment of kidney function and are better predictors of adverse outcome than similar approaches utilising creatinine.

Urinary cystatin C measurements have been proposed as a marker of tubular dysfunction.

3.2 Limitations

Measurement of cystatin C cannot provide information regarding the cause of renal dysfunction. Blood [cystatin C] may also be influenced by thyroid dysfunction. There are reported influences of age, gender, pregnancy, weight, height and genetic variation on cystatin C.

4 Analytical considerations

4.1 Analytical methods

Cystatin C is measured using particle-enhanced turbidimetric (PETIA) or nephelometric immunoassay (PENIA). Latex particles coated with anti-human cystatin C antibodies are incubated with the sample and agglutinate when mixed with the sample containing human cystatin C. The change in absorbance due to agglutination of the reaction mixture is proportional to the concentration of human cystatin C in the sample.

4.2 Reference method: no single reference method stated.

Immunoturbidimetry, nephelometry and diffusion methods have each been proposed.

4.3 Reference materials: ERM-DA471/IFCC. European Commission Joint Research Centre, Institute for Reference Materials and Measurements, Geel, Belgium.

4.4 Interfering substances: spectral and chemical interferences will vary between manufacturers and methods. For example, the Abbott Diagnostics PENIA is unaffected by the following interferents up to the concentrations stated: bilirubin, conjugated (1129 $\mu\text{mol/L}$), bilirubin, unconjugated (1026 $\mu\text{mol/L}$), haemoglobin (10 g/L), lipid (10 g/L), rheumatoid factor (300 kU/L).

4.5 Sources of error

Earlier methods (before ~2011) were not traceable to ERM-DA471/IFCC.

5 Reference intervals and variance

5.1.1. Reference interval (adults)

Adult reference intervals are age- and method-specific, but there is a general consensus to use a common reference range between ages of 1 and 50 years. An interval of 0.6–1.1 mg/L is typical. Higher [cystatin C] has been reported >50 years, mirroring the general decline in renal function that occurs, on average, with ageing.

5.1.2 Others

[Cystatin C] are at their highest in full term newborns and decrease over the first week of life. Less significant decreases then occur between the first month to the end of the first year of life. Premature infants have

concentrations higher than those of term newborns. Paediatric reference ranges generally incorporate the period from birth to 1 year.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 49.9%

5.1.3.2 Intraindividual CV: 4.8%

5.1.3.3 Index of individuality: 0.1

5.1.3.4 Analytical CV: 0.9%

5.1.3.5 Critical difference: positive reference change value (RCV) 14% and negative RCV -13%

5.1.4 Sources of variation

Thyroid status influences [cystatin C] independently of GFR, being lower in a hypothyroid state and higher in a hyperthyroid state. Corticosteroid treatment induces cystatin C production.

6 Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation

1. Serum [cystatin C] can be used to assess glomerular function. It can be interpreted as a single numerical concentration in comparison to the reference range or be used in GFR estimating equations.
2. Serum [cystatin C] can be used to monitor renal function and progression of renal disease
3. Serum [cystatin C] is a risk predictor of poor outcome (death and kidney failure)
4. Urinary [cystatin C] can be used as a marker of tubular dysfunction/damage

6.2 Confounding factors

Thyroid status influences [cystatin C] independently of GFR(see 5.1.4).

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

- acute kidney injury
- chronic kidney disease

7.1.2 Investigation of high values

Investigation into the cause of high [cystatin C] (reduced $eGFR_{cystatin\ C}$) requires further investigation as described in National Institute of Health and Care Excellence (NICE) guidance on CKD and AKI. This may include assessment of hydration status, review of any nephrotoxic drugs being administered e.g. gentamicin, testing for infection/sepsis, imaging studies of the kidney and associated structures e.g. bladder, ureters for evidence of a blockage or a mass if relevant. Investigation should also focus on assessment of co-morbidities e.g. blood pressure and blood [glucose], if relevant. Myeloma, amyloidosis, as well as autoimmune conditions e.g. vasculitis, need to be considered as potential causes and investigated appropriately.

7.2 Low values

Decreased serum [cystatin C] currently has no clear clinical significance. In contrast to the low serum [creatinine] seen with decreased muscle

mass, serum [cystatin C] appears to be relatively unaffected by muscle mass.

7.2.1 Causes

Potentially hypothyroidism.

7.2.2 Investigation of low values

If thyroid dysfunction is suspected then measure fT4 and TSH.

7.3 Notes

An acute change in [cystatin C] is likely to indicate AKI/worsening renal function. Increased cystatin C concentration should be further investigated as described in NICE CKD guidance.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

1. Prediction of renal dysfunction: Sensitivity 81% (76–85); specificity of 88% (84–91).
2. Prediction of AKI: Sensitivity 86% (77–92); specificity 82% (74–88)

9 Systematic reviews and guidelines

9.1 Systematic reviews

Numerous reviews and meta-analyses have been published. Several examine the utility of serum cystatin C as a predictive marker of AKI: e.g. Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in Prediction of Acute Kidney Injury: A Systematic Review and Meta-analysis. *Am J Kidney Dis* 2011;58(3):356–365. (*The authors concluded that serum cystatin C appears to be a good biomarker in the prediction of AKI; urinary cystatin C excretion only has moderate diagnostic value.*)

Others have compared serum cystatin C and creatinine in the context of general renal dysfunction:

Roos JF, Doust J, Tett SE, Kirkpatrick CMJ. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children – a meta-analysis. *Clinical Biochemistry* 2007;40(5–6):383–391. (*These authors concluded that the ability of serum cystatin C to rule-in renal impairment (GFR of 60–79 mL/min/1.73 m²) in those where it is suspected; is large and conclusive.*)

9.2 Guidelines

NICE CG182. Chronic kidney disease in adults: assessment and management. Published July 2014 (updated January 2015).

Summary:

- Consider using eGFR_{cystatin C} at initial diagnosis to confirm or rule out CKD in people with an eGFR_{creatinine} of 45–59 mL/min/1.73m², sustained for at least 90 days and a urine albumin:creatinine ratio <3 mg/mmol, and no evidence of abnormalities in other markers of kidney disease.

- Do not diagnose CKD in those with an $eGFR_{\text{creatinine}}$ 45–59 mL/min/1.73m² and an $eGFR_{\text{cystatin C}}$ >60 mL/min/1.73m² and no other marker of kidney disease

9.3 Recommendations

Consider using a cystatin C assay that is calibrated against ERM-DA471/IFCC. Reference: Eckfeldt JH, Karger AB, Miller WG, Rynders GP, Inker LA. Performance in Measurement of Serum Cystatin C by Laboratories Participating in the College of American Pathologists 2014 CYS Survey. Arch Path Lab Med 2015;139(7):888–93

Consider participation in an EQA programme as per NICE guidance.

10 Links

10.1 Related analytes

There are several other markers of kidney dysfunction that can be used in AKI, tubular dysfunction and CKD: creatinine, urea, albumin:creatinine ratio, $eGFR$, neutrophil gelatinase-associated lipocalin (NGAL), α_1 -microglobulin and measured GFR.

10.2 Related tests

$CKD-EPI_{\text{cystatin C}}$, $CKD-EPI_{\text{cystatin C} + \text{creatinine}}$. Both of these GFR estimating-equations incorporate [cystatin C] as a variable. There are several other $eGFR$ equations that incorporate cystatin C.

Author: Ceri Rowe
20.ix.2017