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AMPATHCHAT

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Cystatin C: an alternative renal function marker

Introduction

The prevalence of chronic kidney disease (CKD) and end-stage renal disease is increasing worldwide. Initial diagnosis relies on estimation of the glomerular filtration rate (GFR), and examination of urinary sediment and protein-excretion to establish the presence of kidney damage. Estimation of the GFR is used to assess the degree of kidney impairment and follow the progress of the disease. GFR is also important for dose adjustment of medications with narrow therapeutic windows such as cytotoxic drugs.

Early detection of progressive kidney disease is important because of the availability of therapies, particularly blood pressure lowering with angiotensin-converting enzyme inhibitors, which can slow the rate of progression in many patients.

Criteria for the diagnosis of CKD are either a GFR less than 60 ml/min/1.73 m^2 or the presence of markers of kidney damage (e.g. albuminuria or urinary sediment) regardless of GFR, for three months or longer[1]. Please refer to *AmpathChat* 18 for more detailed information.

Estimation of the GFR

The gold standard for estimation of the GFR is measurement of the urinary clearance of an ideal filtration marker, such as inulin. This is, however, cumbersome, expensive and not readily available. The normal value for GFR depends on age, sex and body size, and is approximately 130 and 120 mL/min/1.73 m^2 for men and women, respectively, with considerable variation even among individuals with normal renal function.

The most common routine methods for estimation of the GFR are determination of the creatinine clearance or estimating the GFR using an equation. Both are based on creatinine, an endogenous marker of renal function, which can only be used when kidney function is stable. Because of a delay in the accumulation of endogenous markers after the onset of acute kidney injury, it does not initially reflect the GFR accurately.

Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat. Although it is freely filtered by the glomerulus, and not reabsorbed, there is significant proximal tubular secretion, resulting in an overestimation of the true GFR by 10% to 20% when using creatinine clearance for GFR assessment. As the GFR decreases, tubular secretion increases even more, leading to a blunting in the expected rise of creatinine[2]. There are numerous other clinical and analytical factors that affect creatinine measurement, as summarised in Table 2[1].

Table 1: GFR categories in CKD

GFR category	GFR (ml/min/1.73m^2)	Terms
G1*	≥ 90	Normal or high
G2*	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

* In the absence of evidence of kidney damage, GFR category G1/G2 does not fulfill the criteria for CKD (Kidney International Supplements 3, 2013: 19–62)

Table 2: Non-GFR factors affecting creatinine levels and measurement

Factors affecting creatinine generation • Race or ethnicity other than US or European black and white • Extremes of muscle mass or body size • Diet and nutritional status (high protein diet, creatine supplements, ingestion of cooked meats) • Muscle-wasting diseases • Hyperthyroidism (decrease) or hypothyroidism (increase)
Factors affecting tubular secretion of creatinine • Decrease by drug-induced inhibition: trimethoprim, cimetidine, fenofibrate
Factors affecting extrarenal elimination of creatinine • Dialysis • Decrease by inhibition of gut creatininase by antibiotics • Increase by large volume losses of extracellular fluids
Interference with creatinine measurement • Spectral interferences (e.g. bilirubin, some drugs) • Chemical interferences (e.g. glucose, ketones, bilirubin, some drugs)

Kidney International Supplements 3, 2013: 19–62

Cystatin C

Cystatin C is a low molecular weight (13,250 kD) cysteine proteinase inhibitor that is produced by all nucleated cells at a fairly constant rate throughout life. It is freely filtered by the glomerulus, and completely reabsorbed and catabolised in the proximal tubules, not entering the final excreted urine, making it an ideal marker of glomerular filtration rate (GFR), with the serum concentration being inversely related to the GFR.

Cystatin C is less subjected to the effect of age, gender and race than creatinine, and is also less affected by muscle mass and diet. Cystatin C has been reported to be a more accurate marker for acute kidney injury and better at estimating small changes in GFR, as blood levels of Cystatin C equilibrates more quickly than creatinine[3].

There are, however, a few non-GFR factors that influence Cystatin C generation that should be considered when interpreting Cystatin C results (see Table 3).

Table 3: Non-GFR factors affecting Cystatin C levels

Increased Cystatin C Hyperthyroidism[4] Obesity (increased body fat or BMI)[5] Diabetes (average 8.5% higher)[6] Inflammation (higher CRP or WBC, lower albumin)[6] Current cigarette smoking[7] Corticosteroids or other immunosuppressants[8]
Decreased Cystatin C Hypothyroidism[4] Age (4.3% lower for every 20 years of age)[1,6] Female sex (use sex-specific reference ranges)[6]

Although disorders of thyroid function affect the Cystatin C production rate, the majority of patients will still have values within the reference range and GFR estimation would still be accurate[4]. The same is true for obesity[5].

Because corticosteroid or immunosuppressant administration may increase Cystatin C, it is of limited use in oncology and transplant recipients[8].

Current recommendations for GFR estimation[1,2]

- Use a GFR estimating equation to derive the estimated GFR from serum creatinine ($eGFR_{creat}$) or Cystatin C ($eGFR_{cys}$) rather than relying on the serum concentration alone.
- Combining both the serum creatinine and Cystatin C into a single eGFR equation ($eGFR_{creat-cys}$) appears to consistently provide a more precise estimated GFR than equations that use either creatinine or Cystatin C alone, and improves both the accuracy and precision of the estimated GFR.
- Understand the clinical settings in which $eGFR_{cys}$ and $eGFR_{creat-cys}$ are less accurate.
- In patients with muscle-wasting or chronic illness, eGFR based on cystatin C ($eGFR_{cys}$) will be more accurate than a creatinine-based eGFR ($eGFR_{creat}$).
- Because of the wider availability and lower cost of creatinine determinations, the 2013 KDIGO guidelines on CKD recommend using the CKD-EPI creatinine-based estimated GFR ($eGFR_{creat}$) as an initial test.
- Cystatin C determination should be considered as confirmatory or alternative test in the following situations:
  - Adults with $eGFR_{creat}$ 45–59 ml/min/1.73 m^2 who do not have markers of kidney damage (such as albuminuria or radiologic abnormalities) if confirmation of CKD is required.
  - People with factors that potentially interfere with creatinine measurement, including high or low muscle mass or creatinine intake, e.g. children, the elderly or patients with cirrhosis, serious chronic illness such as chronic heart failure, amputations or neuromuscular disease, or those with a high-protein or vegetarian diet.
  - Kidney donor evaluation.
- If the CKD-EPI equation is used for drug dosing, especially in very large or small patients, the reported estimated GFR (which is usually expressed for a standard body surface area of 1.73m^2) should be corrected for the patient's body surface area. If a corrected eGFR is required, please supply the patient's height and weight and request *Creatinine eGFR corrected* (mnemonic CRC).
- In children, the updated Schwartz formula is used to calculate eGFR from creatinine and the child's height is required – please request a *calculated GFR (Schwartz)* (mnemonic EGFRS).

References:

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