International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Creatinine as a Biomarker of Chronic Kidney Disease

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Abstract:

Chronic Kidney Disease (CKD) is a progressive condition characterized by gradual loss of renal function over time. Early diagnosis is essential to prevent complications and improve outcomes. Serum creatinine is one of the most widely used biomarkers for estimating glomerular filtration rate (GFR), a critical measure of kidney function. Despite its limitations, it remains a cornerstone in CKD detection and monitoring due to its accessibility and cost-effectiveness.

Keywords: Chronic Kidney Disease; Serum Creatinine; Biomarker; Renal Function; Glomerular Filtration Rate; CKD Diagnosis; Nephrology.

Introduction:

Chronic kidney disease (CKD) is a significant public health issue worldwide, affecting over 850 million people and ranking as one of the top causes of morbidity and mortality. It is associated with a higher risk of cardiovascular disease, hospitalization, and premature death, particularly as it progresses toward end-stage renal disease (ESRD) **(1).**

Serum creatinine is a widely used and cost-effective biomarker for evaluating kidney function. It is a breakdown product of creatine phosphate in muscle, produced at a fairly constant rate, and eliminated primarily through glomerular filtration. Because of its availability and clinical utility, serum creatinine is a standard component of renal function panels and is often used to estimate glomerular filtration rate (eGFR) using equations such as MDRD and CKD-EPI **(2).**

Despite its widespread use, creatinine has limitations due to its dependence on non-renal factors such as muscle mass, age, gender, ethnicity, diet, and certain medications. These factors can lead to inaccurate estimations of kidney function, particularly in early stages of CKD or in individuals with abnormal muscle mass (e.g., elderly, malnourished, or amputees) **(3).**

To address these limitations, recent research has focused on using additional biomarkers, such as cystatin C, either alone or in combination with creatinine, to enhance the accuracy of eGFR. Cystatin C is less affected by muscle mass and other confounding variables, making it a useful complement to creatinine in clinical assessment **(4).**

For example, a recent study by **Shlipak et al. (5)** demonstrated that combining creatinine and cystatin C significantly improved the accuracy of CKD diagnosis and patient risk stratification compared to using either marker alone, particularly among diverse populations.

Despite the emergence of newer biomarkers, serum creatinine remains a fundamental and practical indicator in routine clinical practice. Its continued relevance lies in its simplicity, affordability, and extensive validation in epidemiological and clinical settings **(6).**

Physiology

Creatinine is the most commonly used marker of renal function in children and adults. Creatinine originates from the creatine/phosphocreatine pathway. Creatine is synthesized in the kidneys and the liver and stored mainly in striated muscle cells, where it is phosphorylated to phosphocreatine by creatine kinase. In turn, phosphocreatine is used to phosphorylate ADP into ATP when energy demand is high. Both creatine and phosphocreatine spontaneously degrade to creatinine. Besides endogenous creatinine production, dietary intake of cooked meat and fish may contribute to the creatinine pool and affect serum creatinine levels. This also applies to creatine supplements **(7).**

Creatinine is a small molecule with a molecular weight of 113 Da and an iso-electric point of 8.74. Creatinine is freely filtered across the glomerular membrane, making glomerular filtration the principal route of elimination. However, creatinine is also excreted by tubular secretion, the level of which is inversely related to GFR (**8).**

Drugs known to inhibit tubular creatinine secretion are trimethoprim, cimetidine, and fenofibrate. Their use may lead to higher creatinine concentrations that do not indicate a deterioration of glomerular filtration. (**9).**

As a result of tubular creatinine secretion, the rise in serum creatinine may be blunted until GFR has almost halved, a phenomenon denoted as “creatinine-blind range”. This is most prominent in children who have low muscle mass and physiologically low serum creatinine levels. Conversely, if urine leaks into the abdomen or the perirenal space, creatinine will be re-absorbed and lead to falsely elevated serum concentrations. In patients with severe kidney failure, gut creatininase also contributes to creatinine excretion, which can be inhibited by antibiotic therapy and lead to a rise in serum creatinine (**9).**

The volume of distribution of creatinine is total body water. Therefore, creatinine serum concentrations lag behind acute changes in GFR. This is most marked at low GFR when it may take several days until a new steady-state has been reached (**10).**

Methods of measuring creatinine

There are several methods of measuring creatinine. The most common and least expensive Jaffe method uses alkaline picrate, which changes to a red color in the presence of creatinine. This method is hampered by so-called noncreatinine chromogens, which are most relevant at the very low creatinine concentrations typically found in infants. This problem is overcome when using enzymatic creatinine assays. Although comparative studies have shown that the enzymatic methods have less interference, the Jaffe method is still widely used, due to its low cost (**11).**

Neonates in the first week of life have physiologically high serum bilirubin levels due to hemolysis of fetal erythrocytes, underdeveloped hepatic conjugating capacity and an increased enterohepatic cycle. **(12).**

Bilirubin absorbs light in roughly the same spectrum as the chromogens formed in the Jaffe reaction. In the alkaline milieu of the Jaffe reaction, bilirubin is oxidized to biliverdin, which causes a decrease in absorbance at the wavelength of 520 nm used to measure creatinine, while the creatinine-picrate chromogens cause an increase. This leads to underestimation of creatinine concentrations in patients with high bilirubin levels. This is even more so for premature infants. Fortunately, enzymatic assays are far less subject to this interference. Therefore, the use of enzymatic tests for creatinine is mandatory in the neonatal period and should be used preferably in all children because of their lower muscle mass **(12).**

The SI unit of creatinine is μmol/L, while in many parts of the world, creatinine is reported in mg/dL (conversion SI × 0.0113 = mg/dL).

Reference values in children

Until the widespread implementation of isotope dilution mass spectroscopy (IDMS)-based calibration of creatinine measurement, reference values varied between hospitals. The use of the IDMS-based standard has allowed the establishment of uniform reference ranges over the whole age spectrum. Normal values for serum

creatinine levels are highly age-dependent. Neonates have relatively high serum creatinine directly post-partum, reflecting maternal levels due to diaplacental exchange of creatinine. Serum creatinine then drops, reflecting low endogenous production in infancy, with the lowest normal values found at about 2 months of age. From then on serum creatinine levels rise steadily as a result of increasing muscle mass (**13).**

Until puberty there is no clear gender-specific difference, while from the age of 14 normal values in male adolescents are higher than in females. As muscle mass in children is more closely linked to height as opposed to weight or body surface area, eGFR equations based on creatinine use height as a correction factor (**14).**

Unless detailed reference intervals per year of life are used, conversion of measured creatinine concentrations into a creatinine-based eGFR is mandatory for the recognition of impaired renal function in children **(15).**

Considerations regarding the use in children

A major problem with estimating kidney function in the neonatal period is the diaplacental exchange of creatinine between mother and fetus. Because creatinine is a small molecule, it passes the placental wall freely, and there is a high correlation between maternal and neonatal serum levels. This precludes kidney function assessment using creatinine both *in utero* (using cord blood) and directly post-partum, when serum creatinine reflects the kidney function of the mother rather than the newborn. Creatinine is therefore a poor marker for acute kidney injury from perinatal asphyxia. It may take serial measurements during the first days of life to determine if the kidney function of a neonate is normal **(16).**

As in adults, muscle mass largely determines serum creatinine concentrations. This is most relevant for boys during adolescence. As the start of puberty varies by up to 5 years, purely age-related reference intervals may be misleading in patients with very early or late puberty. This may affect the early recognition of acute renal failure using the pediatric RIFLE (risk, injury, failure, loss, and end-stage renal failure) criteria. **(17).**

As the rise from a baseline creatinine concentration is one of the diagnostic criteria, early stages of acute kidney injury are easily missed if this crucial information is not available **(17).**

Other populations at risk when using creatinine are children with anorexia nervosa, malignancy, advanced liver disease or neuromuscular disease (e.g. muscle dystrophy, spina bifida). Also, in children after liver transplantation, GFR is overestimated when using creatinine. This also applies to young children after transplantation of a kidney from an adult donor. These children have extremely low serum creatinine concentrations that could potentially lead to a delayed recognition of allograft dysfunction. In order not to miss early signs of kidney dysfunction in particular in young children, it is imperative to use the enzymatic creatinine assay and when reporting concentrations in mg/dL, to report with two instead of one decimal place, the latter being common practice in many laboratories **(18).**

As the volume of distribution of creatinine is the intra- and extracellular space, there is a considerable time lag until establishment of a new steady state after acute changes in kidney function. This is most marked in newborns in which total body water may be up to 75% of body weight as opposed to older children (around 60% of total body weight) **(10).**

Serum creatinine, though the most common biomarker of renal function, has some limitations pertaining to the method of measurement as well as some inherent properties. (**19).**

Jaffe's method of measuring serum creatinine would also measure no creatinine chromogens (including glucose, vitamin C, proteins, acetone [>50 mg/dL], acetoacetate [>20 mmol/L], β-hydroxybutyrate [>25 mmol/L], pyruvate), which could falsely elevate creatinine concentrations. However, the current enzymatic method that measures serum creatinine eliminates the measurement of the chromogens. laboratory uses enzymatic method to measure serum creatinine. Other inherent pitfalls, such as muscle mass determining the value of serum creatinine and a secretory component of creatinine elimination in the renal tubule in addition to filtration, are also present (**19).**

References:

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. *Kidney Int.* 2019;96(5):1048–50.
2. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–12.
3. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! *Nephron Clin Pract.* 2011;118(4):c264–8.
4. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367(1):20–9.
5. Shlipak MG, Boulware LE, Grams ME, et al. Combining Creatinine and Cystatin C to Estimate Glomerular Filtration Rate and Diagnose CKD. *N Engl J Med.* 2023;388(12):1121–1132.
6. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA.* 2012;307(18):1941–51.
7. Baxmann AC, Ahmed MS, Marques NC, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol. 2008;3:348–354.
8. Carambola G, Cupisti A, Bianchi S, Dessì M, Barsotti G. Creatinine clearance and tubular creatinine secretion in chronic renal failure patients. Nephron Clin Pract. 2012;121(3–4):c125–c130.
9. Schreuder MF, Swinkels DW, Kortmann BB, et al. Discrepant results of serum creatinine and cystatin C as a clue to urine leakage after renal transplantation. Transplantation. 2009;88:596–597.
10. Slort PR, Ozden N, Pape L, et al. Comparing cystatin C and creatinine in the diagnosis of pediatric acute renal allograft dysfunction. Pediatr Nephrol. 2012;27:843–849.
11. Schmidt RL, Straseski JA, Raphael KL, et al. A risk assessment of the Jaffe vs enzymatic method for creatinine measurement in an outpatient population. PLoS One. 2015;10:e0143205.
12. Nah H, Lee SG, Lee KS, et al. Evaluation of bilirubin interference and accuracy of six creatinine assays compared with isotope dilution-liquid chromatography mass spectrometry. Clin Biochem. 2016;49:274–281.
13. Pottel H, Mottaghy FM, Zaman Z, et al. On the relationship between glomerular filtration rate and serum creatinine in children. Pediatr Nephrol. 2010;25:927–934.
14. Pottel H, Vrydags N, Mahieu B, et al. Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. Clin Chim Acta. 2008;396:49–55.
15. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–S266.
16. Treiber M, Gorenjak M, Pecovnik Balon B. Serum cystatin-C as a marker of acute kidney injury in the newborn after perinatal hypoxia/asphyxia. Ther Apher Dial. 2014;18:57–67.
17. Plötz FB, Bouma AB, van Wijk JA, et al. Pediatric acute kidney injury in the ICU: an independent evaluation of pRIFLE criteria. Intensive Care Med. 2008;34:1713–1717.
18. den Bakker E, Gemke R, van Wijk JAE, et al. Accurate eGFR reporting for children without anthropometric data. Clin Chim Acta. 2017;474:38–43.
19. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4(11):1832–1843