

Creatinine in Health and Disease: Bridging Physiological Principles with Clinical Practice

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Abstract

Creatinine remains one of the most frequently utilized biomarkers for evaluating renal function in both clinical practice and research. Despite its widespread acceptance, interpretation of serum creatinine requires an understanding of the physiological processes governing its production, distribution, and elimination, as well as the numerous biological and analytical factors that influence its concentration. Variations in age, sex, muscle mass, dietary intake, medications, and laboratory methodologies can significantly affect creatinine values, potentially limiting its accuracy as a standalone indicator of kidney function. Consequently, clinicians must consider these variables when assessing renal status and monitoring disease progression.

This review provides a comprehensive overview of the physiological basis of creatinine metabolism, including its synthesis, renal handling, and mechanisms of excretion. It further examines current laboratory methods for creatinine measurement and discusses their advantages, limitations, and potential sources of analytical variability. The clinical applications of creatinine in estimating glomerular filtration rate, diagnosing acute kidney injury, staging chronic kidney disease, and guiding therapeutic interventions are also explored. In addition, emerging biomarkers, including cystatin C and other novel indicators of renal function, are reviewed as complementary tools that may improve diagnostic precision in selected patient populations.

By integrating fundamental physiological concepts with contemporary clinical evidence, this review highlights both the strengths and inherent limitations of creatinine as a marker of kidney function. A balanced understanding of these aspects can support more accurate interpretation of laboratory findings, facilitate early recognition of renal impairment, and contribute to informed clinical decision-making across diverse healthcare settings.

Keywords: Creatinine; Serum creatinine; Glomerular filtration rate (GFR); Estimated GFR (eGFR)

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Introduction

Assessment of kidney function is fundamental to the diagnosis, treatment, and long-term monitoring of renal disorders. Among the available laboratory biomarkers, serum creatinine remains the most widely used indicator because of its accessibility, low cost, and established role in estimating glomerular filtration rate (GFR). Measurements of serum creatinine are routinely incorporated into clinical practice for the detection of acute kidney injury, staging of chronic kidney disease, adjustment

of medication dosages, and evaluation of disease progression. Although serum creatinine has become an indispensable component of nephrological assessment, its concentration is influenced by numerous physiological and non-renal factors, making careful interpretation essential [1].

Creatinine originates from the metabolism of creatine, a compound involved in cellular energy storage, particularly within skeletal muscle. Since its production is closely related to muscle mass and its elimination primarily depends on renal filtration,

serum creatinine reflects the balance between its generation and excretion. However, factors such as age, sex, ethnicity, nutritional status, exercise, medications, and laboratory methodology may alter creatinine concentrations independently of kidney function. Consequently, clinicians should interpret serum creatinine values in conjunction with the patient's overall clinical condition and complementary laboratory findings [2].

This review discusses the physiological basis of creatinine production, laboratory measurement techniques, clinical significance, non-renal applications, and current limitations. It also highlights the evolving role of creatinine in modern clinical medicine and its relationship with emerging biomarkers for more accurate assessment of renal function.

Physiology and Production of Creatinine

Creatinine is the final metabolic product generated during the normal breakdown of creatine and phosphocreatine, compounds that play an essential role in cellular energy metabolism. Creatine synthesis primarily occurs in the kidneys and liver through a sequence of enzymatic reactions involving the amino acids glycine, arginine, and methionine. Following its synthesis, creatine is transported through the bloodstream to tissues with high energy demands, particularly skeletal muscles, where it is converted into phosphocreatine.

Phosphocreatine functions as a rapidly available energy reserve, supporting the regeneration of adenosine triphosphate (ATP) during periods of increased muscular activity. As part of its normal metabolic cycle, a small proportion of creatine and phosphocreatine undergoes spontaneous, irreversible conversion into creatinine. Because this conversion occurs at a relatively constant rate under stable physiological conditions, serum

creatinine production is generally proportional to total skeletal muscle mass. Once formed, creatinine enters the circulation and is transported to the kidneys for elimination.

Under normal circumstances, creatinine is freely filtered by the glomeruli, with minimal tubular reabsorption and only limited tubular secretion. This physiological characteristic has established creatinine as an important endogenous marker for estimating glomerular filtration rate. Nevertheless, conditions that alter muscle mass, nutritional status, or metabolic activity can substantially influence creatinine production, thereby affecting its interpretation as an indicator of renal function [3].

Laboratory Measurement of Creatinine

Reliable measurement of serum creatinine is essential for accurate evaluation of kidney function. Clinical laboratories commonly employ two principal analytical approaches: the Jaffe reaction and enzymatic assays. The Jaffe method is based on the reaction between creatinine and alkaline picrate, producing a colored complex whose intensity is measured spectrophotometrically. Although this technique is inexpensive and widely available, it is susceptible to interference from endogenous and exogenous substances such as glucose, ketone bodies, bilirubin, proteins, and several medications, which may produce falsely elevated or reduced results.

Enzymatic assays have been developed to improve analytical specificity. These methods utilize sequential enzyme reactions that selectively convert creatinine into measurable products while minimizing interference from non-creatinine compounds. Although enzymatic techniques are generally more accurate and reproducible than the Jaffe method, they are associated with higher operational costs [4].

Parameter	Description	Clinical Significance	Limitations
Creatinine Production	Formed from the non-enzymatic breakdown of creatine and phosphocreatine in skeletal muscle	Reflects muscle metabolism under steady-state conditions	Influenced by age, sex, muscle mass, diet, and physical activity
Renal Handling	Freely filtered by the glomerulus with minimal tubular secretion	Used to estimate glomerular filtration rate (eGFR)	Tubular secretion increases in advanced kidney disease
Jaffe Method	Colorimetric assay using alkaline picrate	Widely available and inexpensive	Susceptible to interference from glucose, ketones, bilirubin, and certain drugs
Enzymatic Assay	Enzyme-based measurement with greater analytical specificity	Improved accuracy and precision	Higher cost than Jaffe method
Reference Methods	IDMS and HPLC	Laboratory standardization and calibration	Limited availability in routine laboratories
Clinical Applications	Diagnosis and monitoring of AKI, CKD, drug-dose adjustment, renal function assessment	Essential biomarker in nephrology	Less sensitive for detecting early kidney dysfunction
Non-Renal Applications	Assessment of muscle mass, nutritional status, frailty, and prognosis	Useful in critically ill and elderly populations	Interpretation affected by non-renal physiological factors

Table 1: Summary of Creatinine Physiology, Measurement, Clinical Utility, and Limitations.

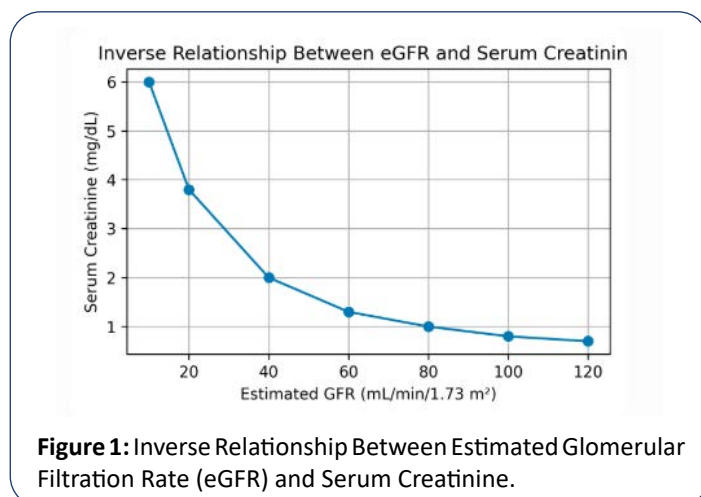
For calibration and standardization, highly precise analytical techniques such as isotope dilution mass spectrometry (IDMS) and high-performance liquid chromatography (HPLC) serve as reference methods (Table 1). Standardization against IDMS has substantially improved comparability of serum creatinine measurements among laboratories worldwide. Despite these advances, minor analytical variability continues to exist because of differences in instrumentation, calibration procedures, specimen handling, and laboratory protocols. Awareness of these methodological considerations is important when interpreting serial creatinine measurements in clinical practice [5].

Clinical and Non-Renal Applications of Creatinine

Although serum creatinine is primarily recognized as a marker of kidney function, its clinical applications extend well beyond the assessment of renal filtration. Because creatinine production largely reflects skeletal muscle metabolism, serum concentrations may provide indirect information regarding muscle mass and nutritional status. Persistently low serum creatinine levels have been associated with reduced muscle mass, frailty, malnutrition, sarcopenia, and poor functional status, particularly among elderly individuals and critically ill patients [6,7].

In intensive care settings, decreased serum creatinine concentrations may identify patients at increased risk of adverse clinical outcomes, including prolonged hospitalization, higher mortality, and delayed recovery. Conversely, elevated serum creatinine frequently reflects impaired renal filtration but may also occur following intense physical activity, increased muscle mass, or consumption of large amounts of cooked meat. Therefore, interpretation should always incorporate the patient's clinical background (Figure 1).

Beyond nephrology, serum creatinine contributes to medication dosing, perioperative risk assessment, cardiovascular disease management, transplantation monitoring, and epidemiological research. Estimated glomerular filtration rate equations derived from serum creatinine remain central to identifying chronic kidney disease, evaluating disease progression, and guiding therapeutic decision-making across diverse medical specialties [8].



Conclusion

Serum creatinine continues to serve as one of the most practical and widely utilized biomarkers for evaluating kidney function. Its physiological relationship with skeletal muscle metabolism and renal filtration provides the basis for its extensive use in estimating glomerular filtration rate and monitoring renal disorders. Nevertheless, numerous biological, pathological, and analytical factors can influence serum creatinine concentrations independently of actual kidney function, reducing its diagnostic accuracy in selected clinical situations such as acute kidney injury, liver disease, severe malnutrition, advanced age, and conditions associated with altered muscle mass.

Appropriate interpretation of creatinine therefore requires consideration of patient-specific characteristics together with standardized laboratory methods and complementary clinical information. Integration of serum creatinine with estimated glomerular filtration rate equations and emerging biomarkers such as cystatin C has enhanced the precision of kidney function assessment. Furthermore, the expanding recognition of creatinine as an indicator of muscle health, nutritional status, and overall prognosis broadens its clinical relevance beyond nephrology. Continued advances in biomarker research and laboratory standardization are expected to improve the accuracy and clinical utility of renal function assessment, ultimately supporting better patient care and outcomes.

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