Evaluation of Serum Creatinine Levels to Diagnose Kidney Function in Patients with Kidney Failure

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Abstract
Background: Kidneys play a key role in maintaining homeostasis within the body and glomerular filtration rate (GFR) is the best measure of kidney function. Direct measurement of GFR using exogenous substances is the gold standard, but it is not practical to do this in clinical practice, and instead clinical practice is heavily dependent on the presence of a metabolic byproduct of muscle, serum creatinine, which is low cost and widely available.
Key points: This research examines the value and usability of serum creatinine as a diagnostic tool in kidney failure patients and draws conclusions based on the results.
Methods: This includes a detailed review of the biochemistry and physiology of creatinine and a discussion of the methods for measuring the concentration in the blood, along with a detailed review of available equations to estimate GFR (eGFR) including the MDRD and CKD-EPI equations.
Results: It has been found that not all the factors influencing the results of serum creatinine reflect its renal origin, as age, sex and muscular mass are all important. A "diagnostic paradox" can also occur in advanced kidney function stage such that the secretion of creatinine into the tubules can be responsible for up to 50% of the loss of creatinine and muscle wasting, or "uremic sarcopenia," may lead to surprisingly stable creatinine levels despite a life-threatening reduction in real GFR.
Conclusions: Serum creatinine is a useful routine marker of renal function, but is not ideal for use in the advanced stages of renal dysfunction, due to biological variation and mathematical inaccuracy in eGFR equations at low levels of filtration. Diagnosis of kidney failure should be based on the context of the interpretation of the actual diagnosis, and other indicators such as Cystatin C may be available for inclusion.

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Keywords: Chronic Kidney Disease, Kidney Failure, Glomerular Filtration Rate, Estimated Glomerular Filtration Rate, Renal Function Assessment

Introduction

Kidney disease is one of the most significant causes of deaths and disabilities among many in many countries; there are many renal diseases which may be categorized as a) Acute kidney failure where the kidneys suddenly and completely lose their function but may regain nearly normal function and b) Chronic kidney failure, where there is a progressive decline in the function of increasing number of nephrons leading to loss of kidney function as a whole.

Kidneys play an important role in removing metabolic waste products from the blood stream, controlling extracellular fluid volume and acid-base and electrolyte homeostasis in the body [2]. Kidney disease is a major source of morbidity and mortality rate throughout the world and it is important to make the correct diagnosis, if possible, and monitor the disease. It is vital to confirm the presence and severity of kidney disease in order to prevent its progression and alleviate its complications [3].

The glomerular filtration rate (GFR) is regarded as the best estimate of the general renal function [4]. Direct measurement of GFR based on exogenous markers such as inulin is the most accurate, but is both invasive and expensive and impractical for routine clinical use[5]. Thus, the estimation of GFR using endogenous biomarkers is an important component of clinical practice. Most commonly used and readily available metabolic marker for the measurement of this is serum creatinine, which is a metabolic waste product of creatine phosphate, muscle energy. It has gained popularity since it is a simple, inexpensive and easily automated test in the clinical laboratory [6].

Although there is use for serum creatinine, it has its drawbacks. It is affected by non-renal variables like age, sex, muscle mass, diet and these can complicate the assessment of kidney function [7]. Moreover, as the correlation between SF and GFR is curvilinear, a significant drop in kidney function can happen before the SF is elevated and exits the normal SR. Particularly in the early stages of chronic kidney disease (CKD). Hence, the value of serum creatinine (SCr) is important for evaluating and interpreting in patients already diagnosed with kidney failure to monitor disease progression and management [8].

In this study, we focused only on serum creatinine as a kidney function marker, its performance and limitations in the above clinical situation.

The Kidney

Kidneys are two organs that are essential to the regulation of the internal environment (homeostasis) of the body. They carry out a variety of regulatory and excretory functions that are very complex and necessary for life. The kidneys are mainly the body's natural filter, removing metabolic waste products from the blood such as the serum creatinine and urea, along with other key nutrients and electrolytes [9]. In addition to its filtering function, the kidney works as a metabolic and endocrine gland and has an important role in the production of red blood cells, regulation of blood pressure, and bone mineral metabolism. The assessment of these functions is key to renal pathology diagnosis especially using the serum creatinine as a proxy to measure renal function [10].

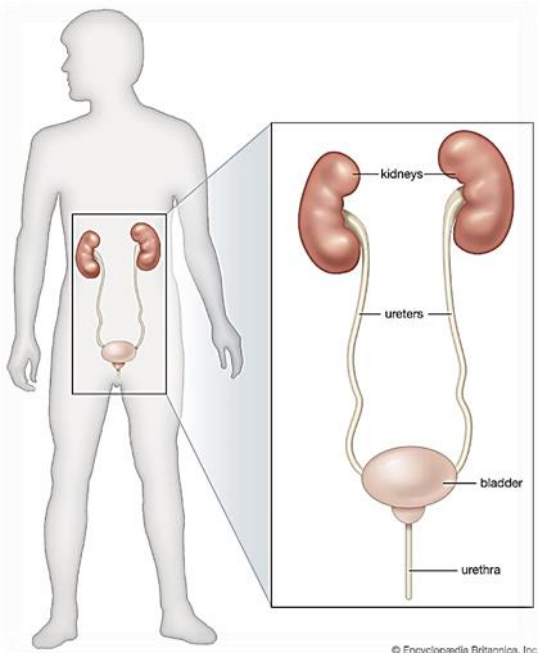

Fig 1: Diagram of the Urinary System.

Gross Anatomy and Location

Kidneys are bean-shaped, reddish-brown structure in the posterior abdominal wall in the retroperitoneal space. They are located on both sides of the vertebral column, usually between T12 and L3. The right kidney is slightly lower than the left kidney, because of the presence of the liver [11].

The average length of an adult kidney is 10 to 12 cm, width of 5 to 7 cm and thickness of 3 cm with a weight of 135 to 150 grams [12]. The lateral margin of kidney is convex and the medial margin is concave and has a deep fissure called renal hilum. The hilum is the site of the renal artery, renal vein, nerves and the ureter going in and coming out of the kidney [13].The interior of the kidney can be subdivided into two sections covered by a hard-fibrous capsule:

The outermost granular part, where most renal filtration takes place is called

1-The Renal Cortex: The outer, granular layer where the majority of renal filtration occurs.

2-The Renal Medulla: Each pyramid opens into the cortex at its base and into the renal pelvis (apical end) which leads to the ureter, carrying urine to the outside [14].

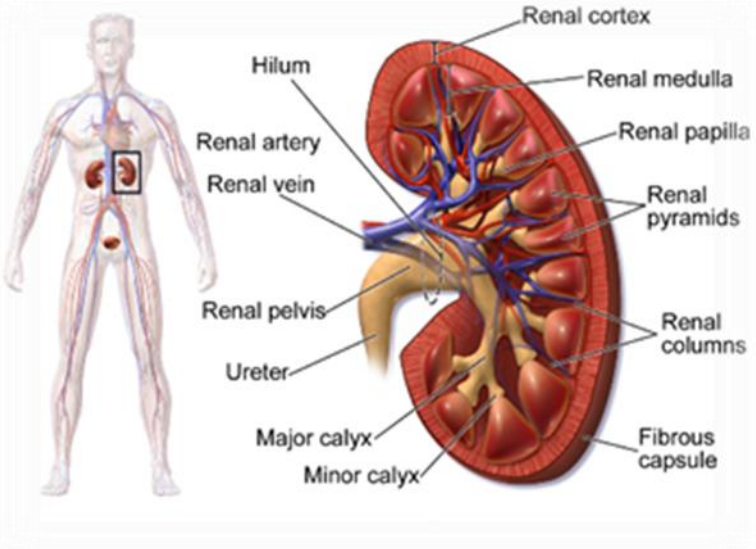

Fig 2: Location and Anatomy of the Kidneys

Microscopic Anatomy

The Nephron: The kidney is composed of structural and functional units called nephron. There are about 1-1.3 million nephrons in each kidney that produce urine. The renal corpuscle and renal tubule are the two principal parts of a nephron [15].

Renal Corpuscle: It is located in the cortex and contains a high-pressure capillary network, the glomerulus, and a double-walled cup that surrounds the glomerulus, called Bowman's capsule. This is the site of the blood plasma filtration. The amount of blood filtered in the glomeruli is called the Glomerular Filtration Rate (GFR) and is clinically estimated by the serum creatinine level [16].

Renal Tubule: A continuous tube which alters the filtrate by reabsorption and secretion. It can be divided into three parts:

- Proximal Convoluted Tubule (PCT): Most reabsorption (water, glucose, amino acids) takes place here.
- Loop of Henle: Runs deep into medulla and plays an important role in concentrating the urine.
- Distal Convoluted Tubule (DCT): Concerned with the adjustment of ion balance and pH.
- Collecting Duct: Receives fluid from multiple nephrons and channels it to the renal pelvis [17].

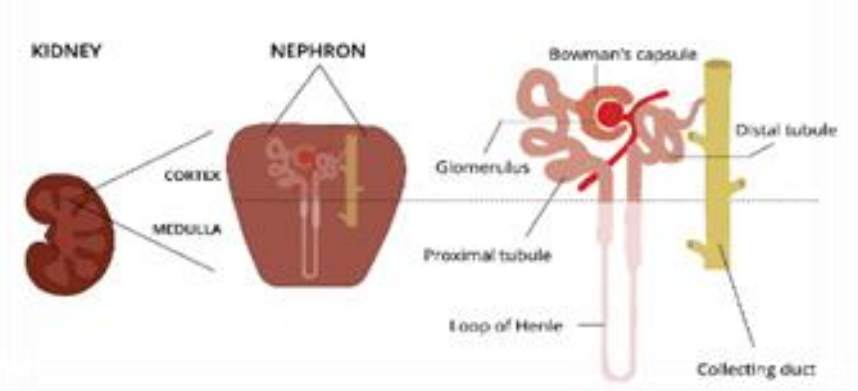

Fig 3: Microscopic Anatomy of the Nephron

Principal Functions of the Kidney:

- The kidneys are involved in a number of physiological processes which are essential for life. These may be divided into excretory, regulatory and endocrine functions [18,19,20].
- **Excretion of metabolic wastes:** Clean-up of blood to remove metabolic wastes that, if not removed, are toxic to the body. Examples of key waste products include urea (from protein), uric acid (from nucleic acid) and creatinine (from muscle metabolism). These substances can't be removed effectively, and that is one of the characteristics of failing kidneys.
- **Regulation of Water/Electrolyte balance:** The kidneys help regulate the volume and composition of body fluids, which includes controlling the excretion of water and ions (sodium (Na+), potassium (K+), calcium (Ca2+) and phosphate).
- **Regulation of Acid-Base Balance:** The kidneys keep the pH of the blood (around 7.4) by reabsorbing bicarbonate ($HCO3^-$) and excreting hydrogen ions (H^+) in the urine.

The kidneys produce some important hormones:

- **Renin:** Controls Blood Pressure and Water balance through the Renin-Angiotensin-Aldosterone System (RAAS).
- **Erythropoietin (EPO):** Stimulates production of red blood cells in bone marrow.
- **Active Vitamin D (calcitriol):** Essential for calcium absorption and bone health.

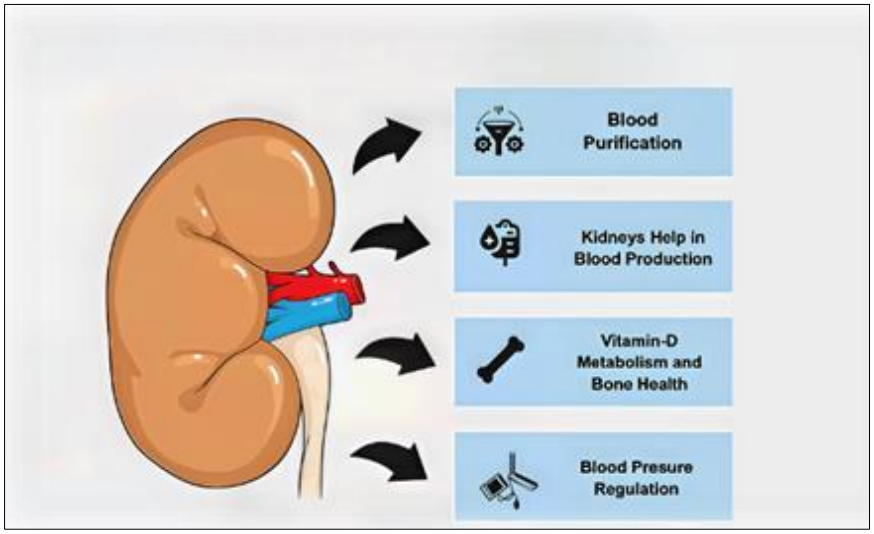

Fig 4: Key Roles of the Kidney

Kidney Failure (chronic kidney disease):

Kidney failure is a late stage of kidney disease (chronic kidney disease or CKD) is characterized by the loss of function of the kidneys and is a serious problem. Persistent abnormalities of kidney structure or function for more than three months that have implications for health are a definition of CKD [21]. The general criteria include a GFR below 60 "mL"\/"min"\/1.73"m" ^2 or kidney damage—Albuminuria, Urine sediment abnormality, Electrolyte and other abnormalities due to tubular disorders, Histology abnormalities, Structural abnormalities detected by imaging, History of kidney transplantation [22].

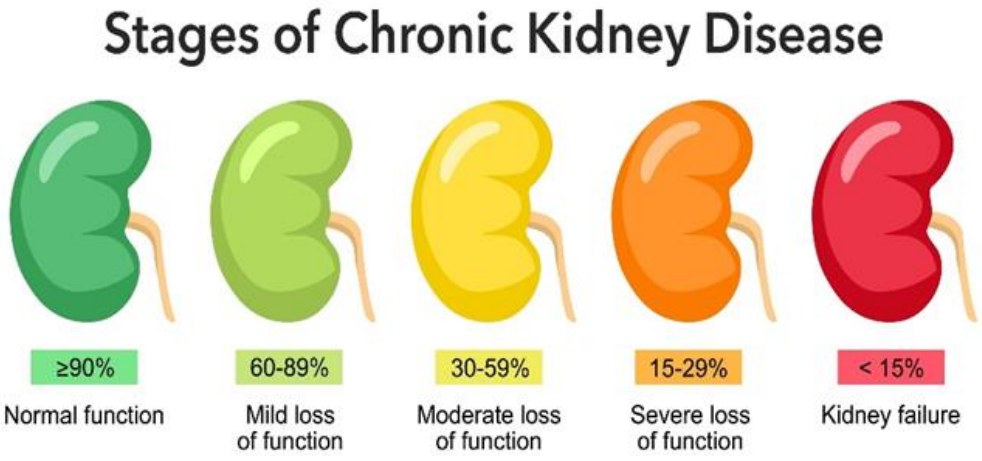

Fig 5: Stages of Chronic Kidney Disease

Kidney failure or End-Stage Kidney Disease (ESKD) is when a person has CKD and the kidneys are less than 15% working. To maintain life at this stage renal replacement therapy (dialysis or transplantation) is required because of the rise in toxins, fluid and electrolytes, resulting in a death by uremia [23].

Classification and Staging:

The classification of CKD has been evolving to better predict prognosis and to help guide management. Currently, KDIGO (kidney disease: Improving Global Outcomes) guidelines are accepted all over the world.

KDIGO has recommended a classification system known as "CGA" which classifies patients according to Cause, GFR category and Albuminuria category [24].

GFR Categories (G Stages):

Based on the estimated GFR (eGFR), CKD is divided into six categories reflecting the severity of functional loss [25]:

Table 1: KDIGO GFR Categories for CKD

Category	Description	GFR Range (mL/min/1.73 m2)
G1	Normal or high	≥90
G2	Mildly decreased	60−89
G3a	Mildly to moderately decreased	45−59
G3b	Moderately to severely decreased	30−44
G4	Severely decreased	15−29
G5	Kidney failure	<15

Albuminuria Categories (A Stages):
Because albuminuria is a strong independent predictor of CKD progression and cardiovascular mortality, it is staged as [26]:

Table 2: Albuminuria Categories in Chronic Kidney Disease

Category	AER (mg/24 h)	ACR (approximate equivalent)		Description
		mg/mmol	mg/g	
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased
A3	>300	>30	>300	Severely increased

Prevalence and Epidemiology:
CKDs are identified as a significant public health issue worldwide, and are becoming more common due to the ageing population and the growing rate of diabetes and hypertension. Around the world, it is estimated that more than 800 million people suffer from CKD. In the world, it is calculated that 10-13% of the general population suffers from CKD. It has become one of the biggest killers; according to the Global Burden of Disease (GBD) study, the ranking of CKD among the leading causes of death over the past 2 decades have markedly increased [27].
Epidemiology is area and social class dependent. High income countries have high prevalence because of lifestyle related risk factors (diabetes and obesity) and low and middle-income countries suffer from the "double burden" of disease from both traditional infectious diseases (such as glomerulonephritis) and growing non-communicable diseases. Renal replacement therapy has become increasingly required for people with kidney failure (Stage G5) and has a large economic cost in health systems worldwide [28].

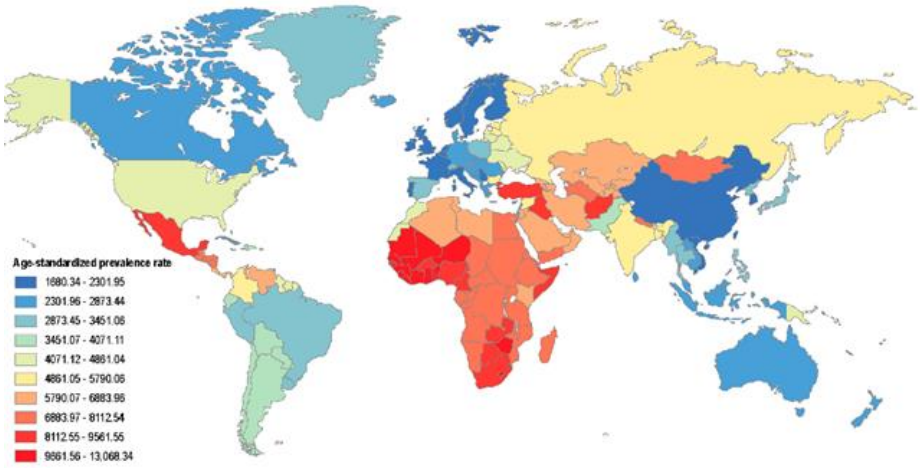

Fig 6: The worldwide age-standardized global prevalence of CKD per 100,000 population in 2016 [75].

The Pathophysiology of Kidney Failure
Pathophysiology of kidney failure is a gradual progressive loss of functional nephrons which is usually irreversible. Whatever the original cause (diabetic nephropathy, hypertension or glomerulonephritis), the common end result is the replacement of normal renal tissue with interstitial fibrosis and glomerulosclerosis [29].
The process usually starts with an injury which first damages the nephrons. The remaining healthy kidneys undergo compensatory hypertrophy and hyperfiltration to keep up the total GFR. This adaptation is beneficial in the short term but eventually the increased intraglomerular pressure and flow lead to mechanical strain and injury to the remaining glomeruli. This results in endothelial injury, proteinuria and activation of pro-inflammatory and pro-fibrotic cytokines (transforming growth factor beta) [30].

All of this maladaptive process leads to:
1. Glomerulosclerosis: Scars in the filtering units.
2. Tubular Atrophy: Hypoxia and toxicity caused by proteinuria leading to loss of tubular cells.
3. Interstitial Fibrosis: When the kidney becomes hard and contracted, with loss of function due to the deposition of collagen in the kidney parenchyma [31].

Complications of Renal Insufficiency
As kidneys fail, the body is unable to excrete waste, regulate fluid volume and make hormones, which causes systemic issues [32-35]:

Volume Overload and Electrolyte Imbalances: Due to the inability to excrete sodium and water, there is a risk of volume overload, hypertension, and edema. A potentially

fatal complication of hyperkalemia (high serum potassium) can lead to cardiac arrhythmias.

Metabolic Acidosis: The kidneys are unable to excrete the acids produced by the body's metabolism daily, so the pH of blood decreases, causing the bone and muscle tissue to deteriorate.
Impaired activation of Vitamin D and impaired phosphate retention causes Hypocalcemia and secondary

Hyperparathyroidism: Mineral and Bone Disorders (CKD-MBD). This leads to weak bones and fractures, or renal osteodystrophy.

Anemia of Chronic Disease: As the kidneys become impaired, they make less of a hormone, erythropoietin (EPO), needed for the production of red blood cells, which leads to normocytic, normochromic anemia.

Cardiovascular Disease: This is the most common cause of death in CKD patients. Vascular calcification, hypertension and chronic inflammation lead to the exacerbation of atherosclerosis and heart failure.

Uremic Syndrome: Advanced kidney failure results in production of uremic toxins, which affect almost every organ in the body, such as nausea, vomiting, uremic encephalopathy (confusion, seizures) and platelet dysfunction (bleeding).
Renal Function Evaluation: The most commonly-used endogenous marker of kidney function is serum creatinine. The ease with which it can be measured, and that it is inversely related to the Glomerular Filtration Rate (GFR) have led to its widespread use in clinical practice. A knowledge of the biochemistry, physiology and limitations of creatinine is a prerequisite to the accurate diagnosis and management of kidney failure patients [36].

Creatinine, Biochemistry and Metabolism of:
Creatinine is a cyclic anhydride of creatine (C4H7N3O). It is the end-product of creatine phosphate metabolism, mainly in skeletal muscle [37].

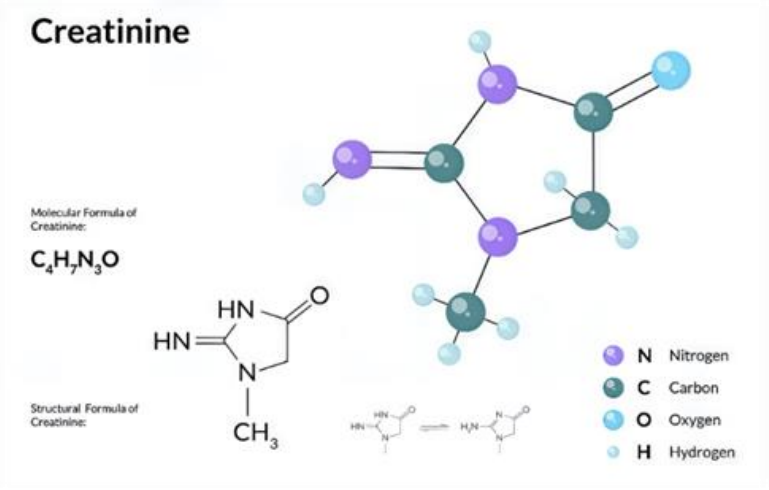

Fig 7: The Chemical Structure and Formula for Creatinine, A Breakdown Product of Creatine Phosphate Found in Muscle Tissue.

The production of creatine
involves the conversion of amino acids (arginine, glycine and methionine) to creatine in the liver and kidneys, and then the movement of creatine to the muscle tissue where it is converted to creatine phosphate, a high-energy phosphate molecule which stores energy.

Dehydration
without enzyme catalysis, of creatine and creatine phosphate, to form creatinine, is irreversible and is called conversion. This conversion takes place at a relatively steady rate (~1-2% of the total creatine pool per day).

Determinants
Because the total creatine pool is proportional to total muscle mass, the daily production of creatinine is biologically determined by the individual's muscle mass. Consequently, males generally produce more creatinine than females, and young adults more than the elderly [38, 39].

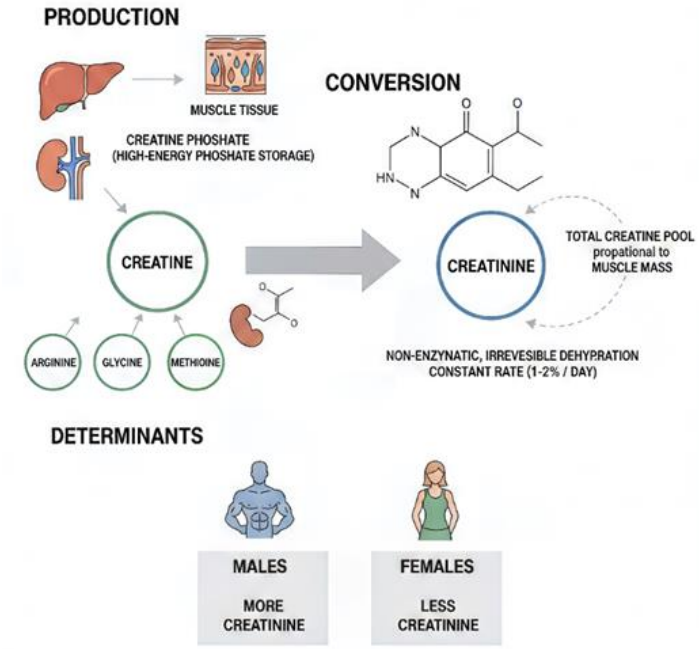

Fig 8: Creatine and Creatinine Metabolism and Determinants of Creatinine Production.

Physiology of Creatinine Filtration

The renal handling of creatinine makes it a useful, though imperfect, marker for GFR [40,41]:

Filtration

Creatinine is a small molecule (113 Da) that is freely filtered across the glomerular basement membrane. Its concentration in the glomerular filtrate is essentially the same as in the plasma.

Reabsorption

Creatinine is not reabsorbed by the renal tubules.

Secretion

A small but significant fraction (approximately 10–20%) of urinary creatinine is actively secreted by the proximal tubular cells via the organic cation secretory pathway.

- **Clearance:** Due to this tubular secretion, the renal clearance of creatinine is about 10-20% higher than the true GFR. A greater percentage of secreted creatinine will be present as GFR falls (in kidney failure), and this may result in an overestimation of the remaining kidney function.

Diagnostic Utility

- **GFR Estimation:** Serum creatinine is the major variable used as a component of equations to estimate GFR (eGFR) which is the standard method of staging chronic kidney disease (CKD).
- **Trend Analysis:** Very useful for observing change over time in the kidney function. A two-fold increase in serum Cr is approximately 50% decrease in GFR.
- **Acute Kidney Injury (AKI):** Rapid increases in serum creatinine are the defining criteria for diagnosing AKI (e.g., KDIGO criteria: increase of ≥ 0.3 mg/dL within 48 hours) [42,43].
- The serum creatinine level cannot be used to accurately assess the severity of the kidney's function.
- **The "Blind Area:** Serum creatinine is not a good indicator of early kidney damage. GFR decreases by about 50% before the serum creatinine level exceeds the upper limit of the normal range, due to the exponential relationship between creatinine and GFR.
- **The lag Phase:** With acute injury, there is a lag in the accumulation of serum creatinine. Levels can take up to 24-48 hours to be representative of the loss of GFR, which may result in delayed diagnosis.

The above-mentioned tubular secretion maintains serum creatinine at lower levels than it would if it were not secreted by the tubules, thus tubular secretion is a physiological mechanism that allows the underestimation of renal impairment severity until its capacity reaches a saturation point [44,45].

Creatinine Is Used to Diagnose Kidney Function

A Single Creatinine Test Is Not Enough to Diagnose Kidney Function. It Requires

- **Normalization:** Using equations to adjust serum creatinine to eGFR based on age, sex and race.
- **Contextualization:** Interpreting the value in the context of patient's muscle mass and clinical status.
- **Clearance Measurement:** In uncertain cases (e.g., amputees, starvation), a 24-hour urine collection for Creatinine Clearance (CrCl) may be performed to measure filtration directly, although this is prone to collection errors [46, 47].

Discussion

The Paradox of Serum Creatinine in Advanced Kidney Failure

Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD) in developed countries, including the United States. It is considered a microvascular complication and occurs in both diabetes mellitus type 1 (T1DM) and diabetes mellitus type 2 (T2DM).

In early-stage kidney disease, the primary limitation of serum creatinine is the "blind area," where substantial nephron loss

occurs before serum creatinine levels rise above the normal reference range. However, in advanced kidney failure, the diagnostic challenge inverses. The relationship between GFR and serum creatinine is exponential; thus, at very low GFR levels (e.g.,<15 mL/min/1.73m²), even minimal changes in absolute GFR result in dramatic, exponential spikes in serum creatinine concentration [48]

While this makes serum creatinine highly sensitive to minor fluctuations in remaining renal function at the end stages of the disease, it also magnifies the impact of non-renal variables. Furthermore, the physiological phenomenon of tubular secretion becomes a major confounder. In healthy individuals, proximal tubular secretion accounts for approximately 10-20% of creatinine clearance. As the GFR falls and the number of nephrons able to work decreases, however, the remaining nephrons with intact function will increase their secretory activity in a compensatory manner. During more severe kidney failure, tubular secretion may contribute 50% or more to the elimination of total creatinine. In turn, this hyper-secretion causes the GFR to be overestimated and can lead to a false sense of security for the clinician as to the actual remaining filtration capacity of the patient [49].

Uremic Sarcopenia and Malnutrition: How to Distinguish Their Impact?

The most important confounding factors to consider when assessing the kidney failure based on serum creatinine include the significant changes in body composition that are observed during uremia. Because serum creatinine production is proportional to the amount of skeletal muscle mass, any disease that decreases the amount of skeletal muscle will decrease serum creatinine, regardless of kidney function.

Patients with advanced kidney failure frequently suffer from Protein-Energy Wasting (PEW) and uremic sarcopenia. The accumulation of uremic toxins, chronic metabolic acidosis, systemic inflammation, and insulin resistance inherent to ESKD lead to an accelerated catabolism of muscle protein [50].

This creates a dangerous diagnostic paradox: as a patient's kidney disease progresses toward terminal failure, their muscle mass simultaneously declines. The decrease in creatinine production due to muscle wasting can perfectly offset the decrease in creatinine clearance caused by failing kidneys. As a result, a patient's serum creatinine level may appear deceptively "stable" over several months, masking a precipitous and life-threatening decline in actual GFR. Clinicians evaluating a frail, sarcopenic patient with kidney failure must recognize that a serum creatinine level of 4.0 mg/dL may represent a significantly worse GFR than the same value in a muscular individual [51].

Fluid Status and Volume Overload

The inability to regulate extracellular fluid volume is a hallmark of kidney failure. Patients with Stage G5 CKD frequently present with volume expansion, edema, and in severe cases, anasarca. The volume of distribution for creatinine is total body water. Therefore, in a state of severe fluid overload, the serum creatinine concentration is artificially diluted. This hemodilution can mask the severity of the renal impairment. If, for example, the dialysis session is made very diuretic or ultrafiltrating, additional fluid will be removed from the body, thus decreasing the amount of fluid in the serum and leading to an apparent "s

A significant increase in serum creatinine ("pike"). This post dialysis rise is not necessarily considered a further decline of the function of the filtering apparatus, but merely correction of the volume of distribution.

Failure to account for the patient's hydration and volume status can lead to widespread misinterpretation of kidney function trajectories in the peri-dialysis period [52]

Limitations of eGFR Equations in the ESKD Population

The widespread adoption of estimating equations like the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) has standardized the classification of CKD. However, these equations were predominantly validated in populations with mild to moderate CKD (G2-G4). They tend to be very imprecise at the very low end of GFR (<15 mL/min/1.73m^2). In patients with kidney failure, there is increased bias and decreased accuracy associated with eGFR equations [53, 54]:

Overestimation of GFR: a number of eGFR equations tend to systematically overestimate the actual measured GFR by virtue of the maximal tubular secretion and common muscle wasting in ESKD.

Imprecision: 95% confidence intervals for eGFR equations are very wide at low values of GFRs. An eGFR reported as 10 mL/min/1.73m^2 might correspond to a true GFR anywhere between 5 and 15 mL/min/1.73m^2. When it comes to deciding to start lifelong dialysis, 5 mL/min is a huge difference.

Comparative Analysis with Alternative Biomarkers

- **Cystatin C**

Cystatin C is a low-molecular-weight protein produced at a constant rate by all nucleated cells in the body. Unlike creatinine, it is freely filtered by the glomerulus, completely reabsorbed, and catabolized by the proximal tubular cells, with no significant tubular secretion. Most importantly, Cystatin C production is independent of muscle mass, age, and dietary protein intake [55].

In patients with kidney failure, especially those exhibiting significant muscle wasting, amputations, or severe malnutrition, Cystatin C provides a far more accurate reflection of true GFR. EGFR based on equations that incorporate both serum creatinine and Cystatin C (CKD-EPI -CysC) have been shown to be the most accurate method for eGFR across all stages of kidney disease and are superior to either marker alone in predicting poor outcomes and mortality [56].

- **Blood Urea Nitrogen (BUN)**

Urea is another waste product that is filtered by the kidneys, but is a less accurate indicator of the GFR than creatinine. Protein intake, catabolic states, gastrointestinal bleeding and hydration status are all important factors affecting urea levels. In more severe kidney failure, however, BUN is still an important ancillary test. The clinical symptoms of uremia (nausea, encephalopathy, pericarditis) are more closely related to high levels of BUN than to creatinine. Thus, creatine can estimate the filtration rate while BUN can be used as an index of the toxicity of kidney failure [57].

Clinical Implications for Patient Management

- **The Timing of Dialysis Initiation**

Historically, the decision to initiate dialysis was heavily weighted upon reaching a specific serum creatinine or eGFR threshold (e.g., eGFR<10 mL/min/1.73m²). However, the unreliability of creatinine in patients with extreme muscle wasting led to premature initiation of dialysis in some frail patients. The landmark IDEAL (Initiating Dialysis Early and Late) study demonstrated that starting dialysis "early" based strictly on an eGFR number provided no survival benefit over a "late" start driven by clinical symptoms [58].

- **Pharmacokinetics and Medication Dosing**

In stage G5 CKD, the therapeutic window for many medications narrows drastically. Overdosing renally cleared medications (e.g., gabapentin, specific antibiotics, or low-molecular-weight heparins) can lead to fatal toxicity. If a clinician relies on an eGFR that is falsely elevated due to the patient's low muscle mass, they risk prescribing a dangerously high dose of medication. In patients with kidney failure, particularly those at extremes of body weight, verifying the eGFR with a 24-hour urine creatinine clearance or utilizing a Cystatin C-based estimation is strongly recommended for critical drug dosing [59].

Conclusions:

Biological vs. Clinical Accuracy:

- Serum creatinine is a convenient but inherently flawed surrogate for kidney function because its concentration is determined by the balance of muscle production and renal secretion, rather than glomerular filtration alone. The Sarcopenic Mask: In the terminal stages of kidney disease, the simultaneous decline of kidney function and muscle mass can result in "stable" creatinine levels, creating a false sense of security while the patient reaches a critical uremic state.
- Standard equations for estimating GFR, such as MDRD and CKD-EPI, are less mathematically accurate and have higher levels of bias in the low range (<15 mL/min/1.73m²), where clinical decisions about dialysis are most important.
- Future Paradigms: The next step in kidney function assessment will be to shift from endogenous biomarkers to point-of-care, real-time GFR measurement using non-invasive fluorescent tracers which will eliminate all confounding factors of creatinine metabolism altogether.

Recommendations

A comprehensive assessment of renal function should be based on more than serum creatinine in patients with renal failure. The following are clinical paradigms for the future:

Multi-marker Panels: combination of serum creatinine with Cystatin C and new novel tubular damage markers, giving an overall assessment of the glomerular filtration and tubular integrity.

Objective Muscle Mass: Assessment: Using bedside assessment (such as Bioelectrical Impedance Analysis (BIA) or specific ultrasound, the amount of skeletal muscle can be assessed and then this value can be used for patient-specific, dynamic correction of creatinine-based eGFR equations.

Real-time GFR Measurement: Development of non-invasive, non-venipuncture fluorescent tracers of real-time GFR instead of complete reliance on endogenous surrogates, which require 24-hour urine collection.

References

1. Naser LA, Abdukaziz B, Alhamad A. A comparative study of cytokines, vitamin D and renal function in diabetic nephropathy patients in Thi-Qar Province, Iraq. 2025. doi:10.1063/5.0320056.
2. Treacy O, Brown NN, Dimeski G. Biochemical evaluation of kidney disease. Transl Androl Urol. 2019;8(Suppl 2):S214-S223.
3. Xie K, Cao H, Ling S, Zhong J, Chen H, Chen P, *et al*. Global, regional, and national burden of chronic kidney disease, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Front Endocrinol (Lausanne). 2025;16:1526482. doi:10.3389/fendo.2025.1526482.
4. George C, Echouffo-Tcheugui JB, Jaar BG, Okpechi IG, Kengne AP. The need for screening, early diagnosis, and prediction of chronic kidney disease in people with diabetes in low- and middle-income countries: a review of the current literature. BMC Med. 2022;20(1):247.
5. Gounden V, Bhatt H, Jialal I. Renal function tests. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
6. Ávila M, Mora Sánchez MG, Bernal Amador AS, Paniagua R. The metabolism of creatinine and its usefulness to evaluate kidney function and body composition in clinical practice. Biomolecules. 2025;15(1):41.
7. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(4 Suppl):S117-S314.
8. Wang X, Mu J, Ma K, Ma Y. Challenges of serum creatinine level in GFR assessment and drug dosing decisions in kidney injury. Adv Pharm Bull. 2024;14(4):745-758. doi:10.34172/apb.42345.
9. Imenez Silva PH, Mohebbi N. Kidney metabolism and acid-base control: back to the basics. Pflugers Arch. 2022;474(8):919-934. doi:10.1007/s00424-022-02696-6.
10. Pethő ÁG, Tapolyai M, Csongrádi É, Orosz P. Management of chronic kidney disease: the current novel and forgotten therapies. J Clin Transl Endocrinol. 2024;36:100354.
11. Garza FA, Leslie SW. Anatomy, abdomen and pelvis: kidneys. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
12. Hoagland TM. Kidney anatomy [Internet]. Medscape Reference; 2025 Mar 26 [cited 2025 Nov 2[0]. Available from: https://emedicine.medscape.com/article/1948775-overview
13. Al-Mamari SA. Anatomy of the kidney. In: Urogenital Trauma: A Practical Guide. Singapore: Springer Nature Singapore; 2023. p. 3-16.
14. National Cancer Institute. Anatomy of the urinary system: components - kidney [Internet]. Bethesda (MD): U.S. National Institutes of Health; 2025 Jan 5 [cited 2025 Nov 2[2]. Available from: https://training.seer.cancer.gov/anatomy/urinary/components/kidney.html
15. Schwartz GJ, Rashid M. Overview, structure, and function of the nephron. In: Pediatric Critical Care: Text and Study Guide. Cham: Springer International

Publishing; 2021. p. 863-909.
16. Murray IV, Paolini MA. Histology, kidney and glomerulus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
17. Gopalan C, Kirk E. Renal physiology. In: Biology of Cardiovascular and Metabolic Diseases. Elsevier; 2022. p. 123-140.
18. Gupta S, Mandal S, Banerjee K, Almarshood H, Pushpakumar SB, Sen U. Complex pathophysiology of acute kidney injury (AKI) in aging: epigenetic regulation, matrix remodeling, and the healing effects of H2S. Biomolecules. 2024;14(9):1165.
19. Giordano L, Mihaila SM, Eslami Amirabadi H, Masereeuw R. Microphysiological systems to recapitulate the gut-kidney axis. Trends Biotechnol. 2021;39(8):811-823.
20. Schoener B, Borger J. Erythropoietin stimulating agents. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
21. Vaidya SR, Aeddula NR. Chronic kidney disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
22. NHS Choices. Kidney disease [Internet]. London: National Health Service; 2024 Oct 10 [cited 2025 Nov 2[4]]. Available from: https://www.nhs.uk/conditions/kidney-disease/
23. Rout P, Aslam A. End-stage renal disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
24. Iatridi F, Carrero JJ, Cornec-Le Gall E, Kanbay M, Luyckx V, Shroff R, *et al*. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease in children and adults: a commentary from the European Renal Best Practice (ERBP). Nephrol Dial Transplant. 2025;40(2):273-282.
25. National Kidney Foundation. How to classify CKD [Internet]. New York: National Kidney Foundation; 2025 Jan 1 [cited 2025 Nov 2[5]]. Available from: https://www.kidney.org/how-to-classify-ckd
26. Caramori ML, Rossing P. Diabetic kidney disease. In: Feingold KR, Ahmed SF, Anawalt B, *et al*., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.
27. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11. doi:10.1016/j.kisu.2021.11.003.
28. Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health concern: early detection should be focused. Health Sci Rep. 2024;7(3):e2004. doi:10.1002/hsr2.2004.
29. Huang R, Fu P, Ma L. Kidney fibrosis: from mechanisms to therapeutic medicines. Signal Transduct Target Ther. 2023;8(1).
30. Fattah H, Layton A, Vallon V. How do kidneys adapt to a deficit or loss in nephron number? Physiology (Bethesda). 2019;34(3):189-197.
31. Zhang T, Widdop RE, Ricardo SD. Transition from acute kidney injury to chronic kidney disease: mechanisms, models, and biomarkers. Am J Physiol Renal Physiol. 2024;327(5):F788-F805.
32. National Kidney Foundation. Chronic kidney disease (CKD) [Internet]. New York: National Kidney Foundation; 2025 Jan 1 [cited 2025 Nov 3[0]]. Available from: https://www.kidney.org/kidney-topics/chronic-kidney-disease-ckd
33. Hoagland TM. Chronic kidney disease [Internet]. Medscape Reference; 2025 Apr 2 [cited 2025 Nov 2[6]]. Available from: https://emedicine.medscape.com/article/238798-overview
34. UK Kidney Association. UK eCKD guide: CKD staging [Internet]. Bristol: UK Kidney Association; 2025 Jan 1 [cited 2025 Nov 2[6]]. Available from: https://www.ukkidney.org/health-professionals/information-resources/uk-eckd-guide/ckd-staging
35. Francis A, Harhay MN, Ong ACM, Tummalapalli SL, Ortiz A, Fogo AB, *et al*. Chronic kidney disease and the global public health agenda: an international consensus. Nat Rev Nephrol. 2024;20(7):473-485.
36. Kashani K, Rosner MH, Ostermann M. Creatinine: from physiology to clinical application. Eur J Intern Med. 2020;72:9-14. doi:10.1016/j.ejim.2019.10.025.
37. Medeiros MA, Abreu BJ, Lima JP. Assessing creatine-related gene expression in kidney disease: can available data give insights into an old discussion? Nutrients. 2025;17(4):651.
38. Bonilla DA, Kreider RB, Stout JR, Forero DA, Kerksick CM, Roberts MD, *et al*. Metabolic basis of creatine in health and disease: a bioinformatics-assisted review. Nutrients. 2021;13(4):1238. doi:10.3390/nu13041238.
39. Post A, Tsikas D, Bakker SJL. Creatine is a conditionally essential nutrient in chronic kidney disease: a hypothesis and narrative literature review. Nutrients. 2019;11(5):1044. doi:10.3390/nu11051044.
40. Kasozi RN, Meeusen JW, Lieske JC. Estimating glomerular filtration rate with new equations: can one size ever fit all? Crit Rev Clin Lab Sci. 2023;60(7):549-559. doi:10.1080/10408363.2023.2214812.
41. Bjornstad P, Narongkiatikhun P, Benzing T, Fuhrman DY, Inker L, Kestenbaum B, *et al*. A comprehensive framework for kidney function assessment: summary of the National Institute of Diabetes and Digestive and Kidney Diseases Reimagining Kidney Function Assessment Workshop. Kidney Int Rep. 2025;10(9):2919-2936.
42. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, *et al*. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-1749.
43. Goyal A, Daneshpajouhnejad P, Hashmi MF, *et al*. Acute kidney injury. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
44. Hernández Petzsche MR. The pathogenesis of chronic uric acid crystal nephropathy [dissertation]. Munich: Ludwig-Maximilians-Universität München; 2021.
45. González-Nicolás MÁ, González-Guerrero C, Goicoechea M, Boscá L, Valiño-Rivas L, Lázaro A. Biomarkers in contrast-induced acute kidney injury: towards a new perspective. Int J Mol Sci. 2024;25(6):3438.
46. Specialist Pharmacy Service. Calculating kidney function [Internet]. Leeds: NHS Specialist Pharmacy Service; 2024 Oct 10 [cited 2025 Nov 3[0]]. Available from: https://www.sps.nhs.uk/articles/calculating-kidney-function/
47. Sandhu G, Adattini J, Gordon EA, O'Neill N, Bagnis C, Chambers P, *et al*. Aligning kidney function assessment

in patients with cancer to global practices in internal medicine. eClinicalMedicine. 2025;82:103102.
48. Li Q, Huang Y, Zhang L, Duan L, Qian S. Perioperative anemia predicts kidney injury after partial nephrectomy. Investig Clin Urol. 2022;63(5):514. doi:10.4111/icu.2022.0160.
49. Öneç K, Altun G, Sav T. Creatinine decline rate as a predictor of renal recovery after acute kidney injury: a retrospective cohort study. Diagnostics (Basel). 2025;15(22):2904. doi:10.3390/diagnostics15222904.
50. Ávila M, Mora Sánchez MG, Bernal Amador AS, Paniagua R. The metabolism of creatinine and its usefulness to evaluate kidney function and body composition in clinical practice. Biomolecules. 2025;15(1):41. doi:10.3390/biom15010041.
51. Zheng WH, Hu YG, Yu DX, Huang HB. Creatinine-to-cystatin C ratio as muscle assessment tool and predictive value for mortality and sarcopenia in patients with chronic kidney disease: a meta-analysis. Front Nutr. 2025;12:1655488. doi:10.3389/fnut.2025.1655488.
52. Zoccali C, Mallamaci F, Adamczak M, de Oliveira RB, Massy ZA, Sarafidis P, *et al*. Cardiovascular complications in chronic kidney disease: a review from the European Renal and Cardiovascular Medicine Working Group of the European Renal Association. Cardiovasc Res. 2023;119(11):2017-2032. doi:10.1093/cvr/cvad083.
53. Roy R, Raman M, Dark PM, Kalra PA, Green D. Adoption of CKD-EPI (2021) for glomerular filtration rate estimation: implications for UK practice. Nephron. 2025;149(3):133-148. doi:10.1159/000541689.
54. Betzler BK, Sultana R, He F, Tham YC, Lim CC, Wang YX, *et al*. Impact of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) GFR estimating equations on CKD prevalence and classification among Asians. Front Med (Lausanne). 2022;9:957437. doi:10.3389/fmed.2022.957437.
55. Benoit SW, Ciccia EA, Devarajan P. Cystatin C as a biomarker of chronic kidney disease: latest developments. Expert Rev Mol Diagn. 2020;20(10):1019-1026. doi:10.1080/14737159.2020.1768849.
56. Gembillo G, Sessa C, Santoro D. Cystatin C-based equations: enhancing accuracy in kidney function tests for type 2 diabetes. World J Nephrol. 2025;14(3):102756. doi:10.5527/wjn.v14.i3.102756.
57. Hillinger P, Markl-Le Levé A, Woyke S, Ronzani M, Kreutziger J, Schmid S, *et al*. The impact of protein feed on the urea-to-creatinine ratio: a retrospective single-center study. Nutrients. 2025;17(8):1293. doi:10.3390/nu17081293.
58. Rivara MB, Mehrotra R. Timing of dialysis initiation: what has changed since IDEAL? Semin Nephrol. 2017;37(2):181-193. doi:10.1016/j.semnephrol.2016.12.008.
59. Liabeuf S, Berdougo-Tritz J, Augey L, Mbarek A, Jadoul M, Deray G, *et al*. Drug exposure in chronic kidney disease: it is not just about the glomerular filtration rate. Fundam Clin Pharmacol. 2025;39(4):e70037. doi:10.1111/fcp.70037.

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