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CREATININE: MARKER OF KIDNEY INJURY

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ABSTRACT
Normal physiology of an individual is governed by varied factors ranging from age, sex, race, diet and physiological and biochemical functioning of the organ systems. The authors herein would like to highlight and stress upon in detail about the kidneys. The kidneys are important organ in our body which has many functions apart from regulation of the electrolytes and the fluid content of the body as well as the regulation of blood pressure. We wish to discuss the patient's kidney function in context of different disorders and drugs that can affect the tests as well as alter normal kidney function (nephrotoxic). Any alteration in functioning of the kidneys can result in alteration of metabolism and excretion of the drugs, thus resulting in increased levels of the drugs in the blood and increased risk of adverse drug effects, which may be either symptomatic or asymptomatic. An important and reliable indicator of kidney function amongst the parameters are serum creatinine level, decrease in kidney function reflecting as increased serum creatinine.

KEYWORDS: Creatinine, eGFR, factors modifying

INTRODUCTION

Biochemistry of Creatinine

Creatine derived from Greek word "Kreas "meaning "flesh "or "muscle mass" is synthesized from three amino acids, namely glycine, arginine and methionine. Creatinine an anhydride of creatine is not reabsorbed but some are secreted and remaining excreted as such in the urine. The blood levels of creatinine and urinary excretion of creatinine remain more or less constant, provided other factors are not affected.[1,2]

Normal Reference Values[1]

	Serum Creatinine	GFR
Adult Male	0.7 to 1.4 mg/dl	95 to 115 ml/min
Adult Female	0.6 to 1.3 mg/dl	85 to 110 ml/min
Children	0.5 to 1.2 mg/dl	-------

Urinary Creatinine Normal Excretion: 1 to 2 gm/day[2]
Serum creatinine concentration is unaffected by dietary or endogenous factors in normal individuals. Creatinine is rapidly removed from the blood and excreted in the urine.[1,2]

Factors Affecting Serum Creatinine[1,2]

Reducing serum creatinine: Low muscle mass, Females, Malnutrition, Drugs: Thiazide diuretics, Vancomycin, Increasing serum creatinine: old age, Males, Creatine supplements and other fitness supplements, renal diseases: Glomerulonephritis, Pyelonephritis, Renal failure, Urinary obstruction, Congestive cardiac failure, Dehydration, Shock, Drugs: Amphotericin B, Captopril, Cephalosporins, Kanamycin, etc, Muscular dystrophy, Severe diabetes mellitus, Thyrotoxicosis.

Creatinine is eliminated by kidneys through a combination of glomerular filtration and active transport. It can be elevated either due to significant reduction in glomerular filtration rate or obstruction to urine outflow, as about 50% of kidney function must be lost before a rise in serum creatinine can be detected. Therefore, serum creatinine is a late marker of acute kidney injury.[3,4] Similarly, a GFR < 15 ml/min is considered as end stage renal disease. However normal GFR does not exclude the presence of kidney disease, which may be evidenced by the presence of albuminuria or proteinuria (microalbuminuria means < 30 mg/gm of albumin in urine which is an early indicator of kidney disease) or radiological imaging.[5,6]

There are number of markers of acute kidney injury for early diagnosis, which are as follows:[7,8,9,10,11,12,13,14]

- IL-18 (interleukin 18)

- KIM 1 (kidney injury molecule 1)
- L-FAB (liver fatty acid binding protein)
- NGAL (neutrophil gelatinase associated lipocalin)
- NAG (N-acetyl β-D-glucosaminidase)
- Cystatin C
- α- GST (alpha glutathione S- transferase)
- AAP (alanine amino peptidase)
- ALP (alkaline phosphatase)
- γ- GT (gamma glutamyl transpeptidase)
- RBP (retino binding protein)
- TIMP 2 (tissue inhibitor metalloproteinase 2)

Availability of these new markers facilitates early detection of changes in renal function before serum creatinine rises, and as such the identification of patients with evidence of kidney injury without change in serum creatinine in the early stage.[12,13,14,15,16]

False High Creatinine

There is need of accurate measurement of serum creatinine for assessment of kidney function. Both exogenous and endogenous substances have led to false estimate of serum creatinine, which is attributed to factors such as decreased or inhibited tubular secretion of creatinine, interference with serum creatinine assays and increase production of creatinine.[17,18,19]

Drugs like famotidine, ranitidine, trimethoprim, salicylates, calcitriol, and cobicistat[20,21,22] and corticosteroids[23,24] can cause inhibition of tubular secretion of creatinine. Thus, leading to positive interference in creatinine levels and as such affects calculation of GFR. Drugs/endogenous substances that can interfere with creatinine assay are cefoxitin, cefalothin, cefpirome, cefazolin,[27] lidocaine,[28] flucytosine,[29] dopamine, dobutamine,[30] furosemide,[18,32] aspirin,[35,36] cyclosporin[34] acetaminophen, methimazole, streptomycin, ethamsylate,[18,20] S-aminolevilinic acid, calcium dobesilate, glucose, haemoglobin, albumin, pyruvate, creatinine, proteins and lipemic substances can affect the enzymatic methods or Jaffe's method. It is seen that interference with enzymatic method is less frequent, however the Jaffe's method is more cost effective and is frequently interfered by these drugs or endogenous substances.[25,26,31,33]

Drugs Causing Nephrotoxicity

Drugs can cause either Pre, Intra or Post renal damage. In pre-renal damage, blood flow to the kidney or glomerulus is decreased. In intra-renal damage, there may be involvement of Glomerulus, Tubular, Interstitial or Blood vessels within the kidneys and post-renal damage is due to obstruction of urinary tract.[37,38,39]

Nephrotoxic NSAIDS can cause pre-renal damage (chronic interstitial nephrites on long term use) and have to be avoided in patients having decreased GFR, dehydration and hypotension. Sometimes even short course therapy with NSAIDS can induce acute kidney injury from renal underperfusion. Drugs like aminoglycosides cause intra-renal while some anticholinergics can cause post-renal damage due to retention of urine in the bladder. It is important that nephrotoxic drugs be avoided in individuals having decreased kidney functions as when used, they can cause renal impairment.[40,41,42]

Nephrotoxic Drugs And Agents[40,41,42]

- NSAIDS – Ibuprofen, naproxen, higher dose aspirin
- Chemotherapeutic drugs:

azathioprine	Dacarbazine	Methotrexate
bleomycin	Epirubicin	Mitomycin
capecitabine	Etoposide	Nitrosoureas
carboplatin	Fludarabine	Pemetrexed
cisplatin	Hydroxyurea	Pentostatin
cladribine	Ifosfamide	Sorafenib
cyclophosphamide	Lenalidomide	Streptozocin
cytarabine(high dose)	Melphalan	Topotecan

- Aminoglycosides
- Amphotericin –B
- Calcineurin inhibitors
- ACE inhibitors
- Loop and thiazide diuretics
- Penicillin and cephalosporins (cefoxitine)
- Angiotensin 2-receptor blockers
- Warfarin
- Anticholinergic drugs
- Vitamin D3

Measurement of Creatinine, eGFR and Creatinine Clearance

Estimation of serum creatinine is either by enzymatic method or by Jaffe's method.[42,43] The enzymatic method is more sensitive, but because of cost effectiveness the Jaffe's method is widely used. Sudden increase in serum creatinine level from 0.8 to 1.2 mg/dl within 8 hours can reflect the GFR approaching zero in patients with acute renal failure. Serum creatinine level is also determined by muscle mass, height, age, sex and limb amputation. The patient with an amputation and a high normal creatinine level may in fact be a patient with advanced chronic kidney disease.[44,45,46] There has been no validation of MDRD calculator[47,48,49,50] in patients with normal GFR and also may in fact underestimate actual GFR in healthy people.

It is important to recognise early and treat reversible causes of renal disease, thereby slow the progression as well as prevent complications of renal disease and identify patients who may require Renal replacement therapy.

Calculation of eGFR

This is estimated by the equation

MDRD = $186x(\text{creatinine}/88.4)^{-1.154}x(\text{age})^{-0.203}$x (0.742 if female) x (1.210 if black)

Modified Schwartz Formula which is used to calculate GFR in children is derived from the CKiD (chronic kidney disease in children).[52,53]
eGFR = K (height in cms)/serum creatinine mg/dl
K value being 0.413

If in case eGFR value is calculated by local laboratory, the same may be used as it is likely to be more accurate than this formula which cannot take into account local variations in creatinine measurements. The normal GFR for an adult is 90 to 120 ml/min. A GFR is less than 15 ml/min is considered to be end-stage renal failure requiring renal replacement therapy, e.g.: dialysis.

Estimates of GFR can only be based on instances where steady state of serum creatinine value and cannot be used with great precision to estimate GFR when there are variations.[49,50,51]

Creatinine Clearance
Kidney function can be known by estimation of creatinine clearance. Formula for which is as follows by the Cockcroft-Gault equation,

Estimated creatinine clearance (ml/min)
= (140-age in years) x weight*(kg) x constant a / serum creatinine (µmol/L)
Constant a = 1.23 for men, 1.04 for women
*Use ideal body weight if excess body fat, calculated as follows:
Ideal body weight (kg) = constant b + 0.91(height in cm – 152.4 cm)
Constant b = 50 for men, 45.5 for women

Creatinine levels of 24 hours urine sample can also be considered for evaluation of creatinine clearance effectively. This method is considered because exercise, diet and hydration can lead to fluctuations in daily creatinine levels. Creatinine levels can vary even throughout the day for which reason, monitoring them for an extended period of time may needed. A blood test may give a test result of creatinine to be very high. But several measurements of creatinine in succession that show elevated levels could indicate chronic kidney disease. Sudden spike in creatinine levels in presence of other factors may be a warning sign for acute kidney damage or other condition.[50,51,54,55]

CONCLUSION

In reviewing various research articles and other references, the authors have dealt with the normal levels of creatinine along with the factors that can affect creatinine levels and calculation of GFR including level at which dialysis or renal transplant may offer in patient care. The authors also cover various drugs that can be nephrotoxic and the same may require dose reduction or substitution with drugs which are less nephrotoxic or those that are mainly metabolised in liver. Presence of albuminuria is an important indicator of subclinical kidney disease which a general practitioner should bear in mind in order to take necessary precautions during therapy and for early referral to specialised centres. There is a need for awareness about all estimates of serum creatinine in laboratory results which may be due to endogenous substances or drug induced and preventive measures for the same, like collecting fasting blood specimen, selection of correct analytical method for creatinine estimation including based on history obtain from patient like drug intake and lastly as far as possible avoidance of collection of samples from indwelling catheters.

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