A COMPARATIVE STUDY ON ACCURACY OF COCKCROFT-GAULT AND MDRD FORMULAE WITH 24 HOUR URINE CREATININE CLEARANCE IN ESTIMATING GLOMERULAR FILTRATION RATE

Dissertation submitted for

DOCTOR OF MEDICINE

Branch I – GENERAL MEDICINE

April 2015

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI, TAMILNADU.

CERTIFICATE

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY ON ACCURACY OF COCKCROFT GAULT AND MDRD FORMULAE WITH 24 HOUR URINE CREATININE CLEARANCE IN ESTIMATING GLOMERULAR FILTRATION RATE**" is a bonafide work of **Dr.M.RATHINAM** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch-I examination to be held in **April 2015**.

Dr.R.BALAJINATHAN MD.,
Professor,
Department of Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

Dr.S.VADIVEL MURUGAN MD.,
Professor and HOD,
Department of Medicine
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

DEAN

Madurai medical college

Madurai

DECLARATION

I, **Dr.M.RATHINAM**, solemnly declare that, this dissertation "**A COMPARATIVE STUDY ON ACCURACY OF COCKCROFT GAULT AND MDRD FORMULAE WITH 24 HOUR URINE CREATININE CLEARANCE IN ESTIMATING GLOMERULAR FILTRATION RATE**" is a bonafide record of work done by me at the Department of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.R.BALAJINATHAN M.D**., Professor, Department of General Medicine, Madurai Medical college, Madurai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch-I, examination to be held in April 2015.

Place: Madurai

Date: **Dr.RATHINAM.M**

ACKNOWLEGEMENT

I would like to thank **Capt.Dr.B.SANTHAKUMAR, M.sc (F.sc), M.D (F.M), PGDMLE, Dip.N.B (F.M)** Dean, Madurai Medical College, Madurai, for permitting me to utilise the hospital facilities for dissertation.

I also extend my sincere thanks and gratitude to Prof.**Dr.S.VADIVELMURUGAN MD**, Head of the department and Professor of Medicine for his constant support during the study.

I would like to express my deep sense of gratitude and thanks to My Unit Chief, my guide and Professor of Medicine, **Dr.R.BALAJINATHAN MD**., for his valuable suggestions and excellent guidance during the study. I am greatly indebted to my beloved Professors, **Dr.V.T.PREMKUMAR, M.D., Dr.M.NATARAJAN, M.D., Dr.G.BAGHYALAKSHMI, M.D., Dr.J.SANGUMANI, M.D., Dr.C.DHARMARAJ, M.D., and Dr.R.PRABHAKARAN, M.D.,** for their valuable suggestions throughout the course of study.

I would like to express my thanks to nephrology Chief, **PROF.DR.SHANMUAPERUMAL MD DM,** and Assistant prof. **DR.BALAMURUGAN MD, DM,** for his valuable suggestions and excellent guidance during the study.

I thank the Assistant Professors, **Dr.G.GURUNAMASIVAYAM MD., Dr.V.N.ALAGAVENKATESAN, MD, Dr. L.VELUSAMY, MD,** for their valid comments, guidance and suggestions.

I sincerely thank all the staffs of Department of Medicine and Department of Nephrology, Department of biochemistry for their timely help rendered to me, whenever and wherever needed.

I wish to acknowledge all those, including my post graduate colleagues, my parents who have directly or indirectly helped me complete this work with great success.

Last but definitely not the least, I thank all the patients who participated in this study for their extreme patience and co-operation without whom this project would have been a distant dream and I pray God, for their speedy recovery.

CONTENTS

A COMPARATIVE STUDY ON ACCURACY OF COCKCROFT GAULT AND MDRD FORMULAE WITH 24 HOUR URINE CREATININE CLEARANCE IN ESTIMATING GLOMERULAR FILTRATION RATE

***Abstract*:**

Estimation of the glomerular filtration rate (GFR) is important in clinical practice that too in intensive care setting. Most of the antibiotics and drugs that are used in ICU setting are excreted via the kidney. The MDRD formula and Cockcroft Gault equation are most commonly used to calculate GFR. Usefulness of these formulas in clinical setting is dependent on precision and bias. So this study is designed to evaluate these formulas with 24 hour urine creatinine clearance in critically ill patients by calculating correlation coefficient. ***Materials and methods:*** This study was conducted in 100 adult patients of Govt, Rajaji, hospital, Madurai. We estimated Creatinine Clearance by CG and MDRD formula and measured GFR by 24 hrs urine creatinine clearance. Bland Altman plot was used to find the difference between the paired observations. ***Results:*** The mean GFR measured by 24 hours urine creatinine clearance was 44.75ml/min/1.73m2 (95% CI: 41.13 to 48.37). The mean glomerular filtration rate calculated by Cockcroft-Gault formula was 56.48ml/min/1.73m2 (95%CI: 52.45 to 60.51) and by MDRD formula was 48.71ml/min/m2 (95% CI: 44.80 to 52.62). Correlation coefficient for comparison of CG formula/24 hour urine creatinine clearance and MDRD/24 hour urine clearance were 0.90956 with p value of <0.0001 and 0.9303 with p value of <0.0001 respectively. Bias is defined as the mean difference between calculated and measured GFR. In our study bias was 11.73ml/min for Cockcroft-Gault equation and 3.961ml/min for MDRD equation. This indicates overestimation of glomerular filtration rate by these two formulas.

Conclusion: C-G and MDRD equations can be an alternative to the CrCl test for assessing GFR, thus avoiding the need for the cumbersome and expensive GFR test. The MDRD formula had greater validity than the C-G equation.

Key words: Glomerular filtration rate, Cockcroft-Gault formula (C-G), Modification Diet in Renal Disease Formula (MDRD), bland Altman analysis.

INTRODUCTION

Estimation of the glomerular filtration rate is important in clinical practice that too in intensive care setting. Most of antibiotics and drugs that are used in ICU setting are excreted via the kidney. Usually in research GFR is measured by substances completely filtered by the glomerulus without tubular secretion or tubular reabsorption. Commonly used substances for this purpose are inulin, isotopes such as Technetium- 99m diethyl triamine penta-acetic acid (Tc99m DTPA) or chromium 51 Ethylene diamine tetraacetic acids (Cr51 EDTA), iohexol or iothalmate[1].

These methods are not possible in ICU setup particularly in developing countries like India. So serum creatinine is used to calculate GFR. But serum creatinine is dependent on age, sex, muscle mass and type of food consumed. So GFR based on serum creatinine is not accurate to decide about drug dosage and treatment.

GFR calculation by 24 urine creatinine clearance may correct some of the errors due to muscle mass and creatinine generation. But measurement of 24 hour creatinine clearance is not at all possible in treatment decision, because we have to wait for at least 24 hours to get the results[1]. In the meantime kidney function may change. So lot of formulas

was devised to calculate GFR by using serum creatinine, age, sex and body weight.

The MDRD formula and Cockcroft Gault equation are most commonly used to calculate GFR. Cockcroft Gault formula derived from group of white men, based on serum creatinine and age. Females are not included while deriving this formula. Based on expert opinion GFR is reduced by 15% for them. MDRD formula derived from group of outpatients. Some of the studies evaluated these formulas in critically ill patients but with normal creatinine. So application these formulas derived from stable patient needs to be evaluated before applying into critically ill patients.

There are some unique issues with these patients in their hemodynamic instability, rapid change in kidney function, protein catabolic state and battery of medication. These are also affecting the GFR calculation in these patients. Usefulness of these formulas in clinical setting is dependent on precision and bias. So this study is designed to evaluate these formulas in critically ill patients by calculating correlation coefficient[1].

AIMS AND OBJECTIVES

- To compare the glomerular filtration rate calculated by Cockcroft-Gault and MDRD formula with glomerular filtration rate measured by 24 hours urine creatinine clearance.
- By calculating bias and correlation coefficient, to decide about usefulness of these formulas in critical care setting.

REVIEW OF LITERATURE

NORMAL ANATOMY AND PHYSIOLOGY OF KIDNEY

The main function of the kidney is to maintain internal homeostasis and giving suitable environment for cellular metabolism and cellular function. Kidneys achieve these by excreting metabolic waste products, balancing solute and water transport, conserving nutrients and also by maintaining acid-base balance. Kidneys also functioning as a endocrine organ by secreting renin, erythropoietin and 1,25-dihydroxy cholecalciferol (vitamin D) which regulates blood pressure and electrolyte balance, RBC production and calcium metabolism and bone mineral density respectively[2].

ANATOMY

Kidneys are two paired organs situated in the retroperitoneal space along the sides of the vertebral column. They are extending between T12 vertebra to L3 vertebra. Because of liver right kidney situated slightly lower than the left kidney. Each kidney is weighing approximately 125 to 175 grams in male and 115 to 155 grams in female. Length of the kidney is 11 to 12 centimeters, width is 5 to 7 centimeters and thickness is approximately 3 centimeters[2]. Renal artery, renal vein, ureters lymphatics and nerve plexus enters kidneys via the renal hilum which is situated along

the medial surface of the kidney. There is a renal capsule which surrounds the kidney.

After entering into hilum renal artery divides into anterior and posterior branches. Anterior branch divides into three lobar or segmental arteries and supplies the anterior surface of the kidney. The posterior branch of the renal artery supplies the posterior surface of the kidney and very rarely it gives an apical branch. These are end arteries; there are no anastomoses between these arteries.

Kidney consists of outer cortex and inner medulla. There are 8 to 18 renal pyramids in each kidney which are located in the medulla. The apices of the renal pyramid are towards the renal pelvis and forms papilla; bases of the pyramids are towards the cortex. Collecting duct opens into papilla. Cortex contains all the glomeruli and portions of the tubules. The renal cortex is 1 cm thick and extends between the pyramids to form the renal columns of Bertini. From the base of the renal pyramid, at the corticomedullary junction, longitudinal elements termed the "medullary rays" extend into the cortex. These medullary rays are formed by collecting ducts, proximal and distal tubules[2].

Renal pelvis represents upper dilated end of ureter which is lined by transitional epithelium. Two or three major calyces extend from the renal

pelvis, from which several minor calyces extends towards the renal papilla and drain the urine. Lower part of renal pelvis continued as ureter and opens into the bladder. The renal pelvis represents the upper urinary tract and is lined by transitional epithelium. The major calyces which is two or three in number, extends from renal pelvis. From major calyces, several minor calyces extend toward the papillae and drain the urine. The ureters are 28 to 34 cm in length, arise from lower part of the renal pelvis and open into the bladder. The smooth muscle is present in the walls of ureters produces peristaltic movement. With this movement, urine from the kidney drains into the bladder.

THE NEPHRON

The nephron is the functional unit of the kidney, each kidney consist approximately 1.2 million nephrons. The parts of the nephron are the glomerulus, proximal tubule, loop of Henle, distal tubule, and the collecting duct. The nephron develops from metanephric blastema. Embryologically collecting ducts develops from the ureteric bud.

Nephrons are divided into two groups based on length of loop of henle. The loop of Henle consists of thin descending limb and thick ascending limb. Cortical nephrons have short loop of henle and juxta medullary nephrons have long loops.

GLOMERULUS

Glomerulus consists of tuft of capillaries lined by endothelial cells, mesangial cells with mesangial matrix, the visceral and parietal layer of Bowman's capsule with basement membrane. Bowman's space is situated between the visceral and parietal epithelial layers. The diameter of the glomerulus is around 200 μm^3. The glomerulus produces the ultra-filtrate of plasma. The filtering unit consists of endothelium, basement membrane, and the foot processes of the visceral epithelial cells.

Capillaries in the glomerulus is lined by fenestrated endothelial cells, these fenestrations are surrounded by intermediate filaments and microtubules. This glomerulus endothelium has negative charge; this is provided by Podocalyxin. Nitric oxide (vasodilator) and endothelin-1 are synthesized by glomerular endothelial cells. VEGF receptors are seen in the endothelial cells[3]. VEGF is produced by visceral epithelial cells and it increases permeability of endothelial cells by increasing the formation of endothelial fenestrations and also VEGF is essential for survival and repair of endothelial cell in glomerular diseases. Each epithelial layer in the glomerulus has unique structural properties that allow components of the blood to pass through with the exception of blood cells and plasma proteins of molecular weight greater than 70,000. The endothelial cells are the

barrier to prevent the passage of blood components from reaching Bowman's space.

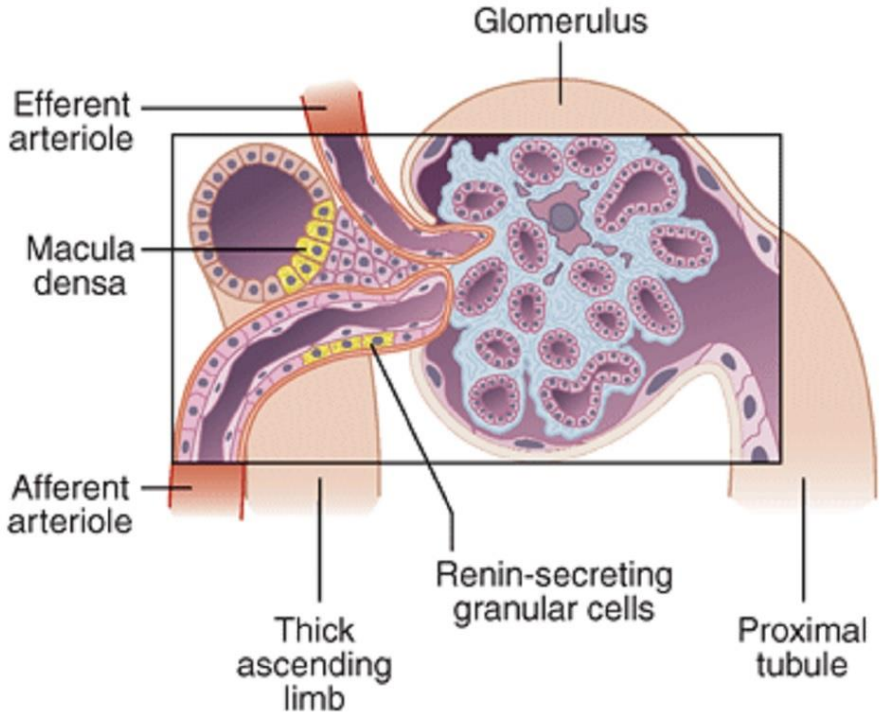


Fig-1 Normal glomerulus

VISCERAL EPITHELIAL CELLS

The distance between two visceral epithelial cell foot processes is 25 to 60 nm. This is filtration slit and is covered by a thin membrane called filtration slit membrane. A central filament is seen in the filtration slit diaphragm. Nephrin is the main constituent of the filtration barrier. NPHS1 gene located in the chromosome 19 codes this nephrin; Mutation of NPHS1 is noticed in congenital nephrotic syndrome of the Finnish type[5]. Nephrin is seen in the visceral epithelial cells particularly in the slit diaphragm.

Deletion of CD2AP, which binds the nephrin to the cytoskeleton, is responsible for congenital nephrotic syndrome. Mutation of the Podocin; a membrane protein that is seen in filtration barrier is responsible for familial steroid-resistant nephrotic syndrome[5]. The foot processes are replaced by cytoplasmic band which is termed as effacement of foot process. Podoplanin maintains shape of foot process. The visceral epithelial cells are responsible for the production and maintenance of the filtration membrane.

PARIETAL EPITHELIAL CELLS

Parietal epithelial cells are squamous epithelial cells. Recent evidences suggest that they are progenitors of podocytes. After injury to podocytes these parietal epithelial cells regenerates and forms podocytes. They also implicated in some form of proliferative form of glomerulonephritis.

MESANGIAL CELLS

Irregularly shaped mesangial cells and its matrix constitute the mesangium. Mesangial cells have dense nucleus and elongated cytoplasmic processes. These processes consist of microfilaments such as actin, actinin and myosin. These cells bridge the gap between glomerulus and basement membrane and prevent distension of capillaries. Mesangial matrix composed of glycosaminoglycans and collagen[4]. Mesangial cells are

specialized form of pericyte; having many characteristics of smooth muscle cells. They are providing support to glomerular capillaries, regulates glomerular filtration rate and synthesizes Mesangial matrix[4].

GLOMERULAR BASEMENT MEMBRANE

The glomerular basement membrane consists of two thin layers the lamina rara externa and the lamina rara interna and a dense layer the lamina densa. Basement membrane composed of type IV collagen. Mutation of the α3, α4, and α5 chains causes Alport's syndrome. Podocalyxin present in the glomerular basement membrane gives its negative charge. Presence of anionic site in the basement membrane is demonstrated by Caulfield and Farquhar with the use of lysozyme. These anionic sites in the basement membrane are made up of glycosaminoglycans such as heparan sulfate[4].

JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is situated where the afferent and efferent arterioles meet the distal convoluted tubule. It is named because of its proximity to the glomerulus. JG apparatus controls function of each kidney. Components of the juxtaglomerular apparatus are macula densa, juxtaglomerular cells and extra glomerular mesangium. Macula densa is formed by cells of the distal convoluted tubule. Macula densa senses the sodium chloride concentration in the tubular fluid and secretes the locally

acting vasoactive substance, there by controls the GFR by changing efferent arteriole diameter as a part of tubuloglomerular feedback[4].

JUXTAGLOMERULAR GRANULAR CELLS

Juxtaglomerular granular cells are present in the walls of the arteriole and extra glomerular mesangial region. They are having characteristics of both smooth muscle cells and epithelial cells. These cells contain renin and its precursor granules.

EXTRA GLOMERULAR MESANGIAL CELLS

Also known as lacis cells or the cells of goormaghtigh situated between the afferent arteriole and macula densa. Functions of the cells are not clearly known. It may be associated with secretion of erythropoietin.

PROXIMAL TUBULE

Proximal tubule is a portion of the nephron which extends from the Bowman's capsule and extends up to loop of henle. It consists of proximal convoluted portion knows as pars convoluta and distal straight portion known as pars recta. Pars convoluta entirely situated in the cortex. It maintains the PH of the filtrate absorbs the most of the filtered components and secretes the creatinine and organic acids[6]. Approximately two-third of

the filtered water, 100% of the glucose and amino acids are absorbed from the proximal convoluted tubule.

LOOP OF HENLE

It is a U shaped portion of nephron situated in between the proximal and distal convoluted tubule. Most important function of the loop of henle is to provide high osmotic gradient inside the medulla by counter current system. With the help of ion channels it creates high concentration in the medulla, so water is absorbed from the filtrate according to osmotic gradient.

DISTAL CONVOLUTED TUBULE

It is situated between the ascending limb of loop of henle and collecting duct of the renal tubule. It maintains the PH, regulates electrolyte balance. Vasopressin acts through the receptors situated in the collecting duct and facilitates water reabsorption. Na+/cl- channels present in the distal convoluted tubules are thiazide sensitive. By inhibiting these channels, thiazide causes luminal Na+ gradient and also diuresis[6].

FUNCTIONS OF THE KIDNEY

A. Maintain water homeostasis.

B. By producing erythropoietin, active form of vitamin D and renin acts as a endocrine organ

C. Regulation of acid base balance.

D. Elimination of metabolic waste products.

E. Excretion of toxic substances from the body.

F. Blood pressure maintenance

G. Catabolism of small peptide hormones

ACUTE KIDNEY INJURY

Acute kidney injury is divided into three types based on aetiology. They are

1) Pre-renal

2) Intrinsic AKI

3) Post renal or obstructive

PRE RENAL AKI

CAUSES

DECREASED INTRAVASCULAR VOLUME

- Blood loss in trauma, operations, upper gastrointestinal bleeding and PPH
- Gastrointestinal fluid loss due to vomiting, diarrhoea, nasogastric aspiration
- Renal loss- osmotic diuresis, diuretics
- Insensible water loss due to fever and burns
- Fluid loss into body cavities in pancreatitis and hypo albuminemic conditions

DECREASED STROKE VOLUME

- Myocardial infarction
- Dilated cardiomyopathy
- Valvular heart disease
- Pericarditis
- Antihypertensive drugs
- Pulmonary embolism

DRUGS

- ACE inhibitors in bilateral renal artery stenosis.
- Usage of NSAIDS in hypovolemic state.

PRE RENAL ACUTE KIDNEY INJURY

It is the most common form of acute renal failure seen in clinical practice. Due to decreased blood supply, kidneys adopt themselves to maintain the intravascular volume. Kidney parenchyma is not affected by this form of renal failure. If adequate blood flow to kidneys is restored, GFR will become normalized. If prerenal form persists for sometime these patients may develop some form of acute tubular necrosis, then prerenal and intrinsic renal injury may overlap.

This form of AKI is seen in conditions such as hypovolemia, systemic vasodilatation such as in anaphylaxis, low cardiac output states and in intrarenal vasoconstriction. Due to hypovolemia there is decrease in effective mean circulatory pressure, which results in activation of baroreceptors that leads to activation of RAAS, sympathetic system and release of ADH from posterior pituitary[7].

Activation these systems results in release of nor-epinephrine, angiotensin II and ADH which in turn causes vasoconstriction of musculo skeletal system, splanchnic circulation, decreases the sweat formation,

decreases the water excretion and increases the thirst in order to maintain adequate blood supply to vital organs such as brain and heart. In very early stages of hypovolemia there is autoregulation by prostaglandin and nitric oxide by which kidneys preserve GFR[7].

Normal GFR is maintained with wide range of blood pressure by varying resistance between the afferent and efferent arterioles, which controls the glomerular plasma flow. Both kidneys receive approximately 20% of the cardiac output[7]. In hypovolemic states there is a decreased blood flow to kidneys, but blood flow to brain and heart is maintained as a part of autoregulation. In early phases of hypovolemia, glomerular filtration pressure is maintained by constriction of efferent arteriole by angiotensin II.

In low perfusion states, dilatation of afferent arteriole occurs to maintain adequate blood flow to the glomerulus. There is increased renal prostaglandin synthesis occurring in hypovolemic states which causes vasodilatation of afferent arteriole. In low perfusion states, there is activation of tubuloglomerular feedback system because of decreased solute load in the distal tubule.

Non-steroidal anti-inflammatory drugs block intrarenal prostaglandin synthesis, so that afferent arteriole vasodilatation in low perfusion states is

blocked. By blocking angiotensin II, ACE inhibitors block the efferent arteriolar constriction in response to decreased glomerular filtration pressure. So autoregulation in renal circulation is severely compromised. Thus both ACE inhibitors and NSAIDs used in combination increases the risk of AKI. It is advisable not to use both these drugs in combination[8].

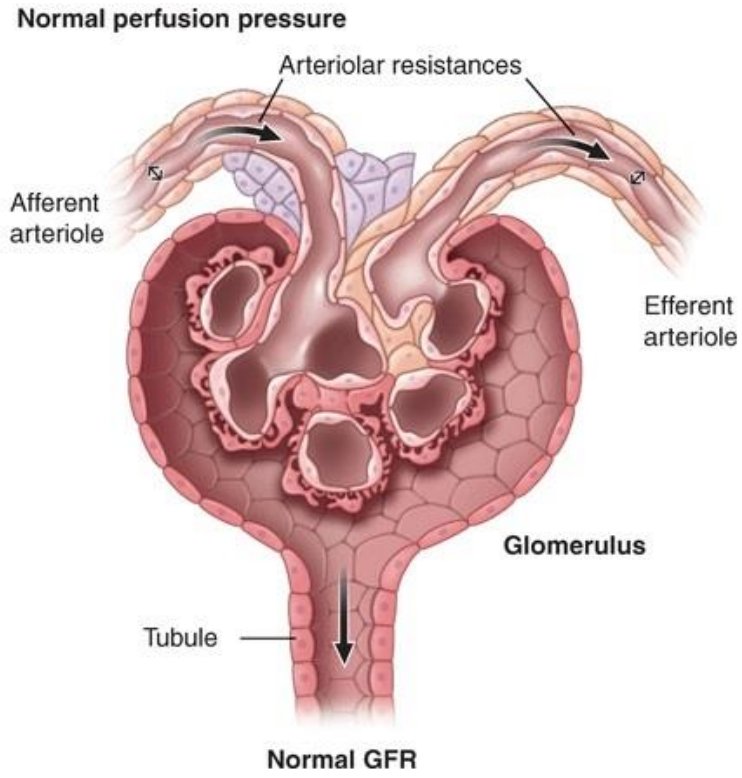


Fig-2 Normal Renal perfusion pressure[8]

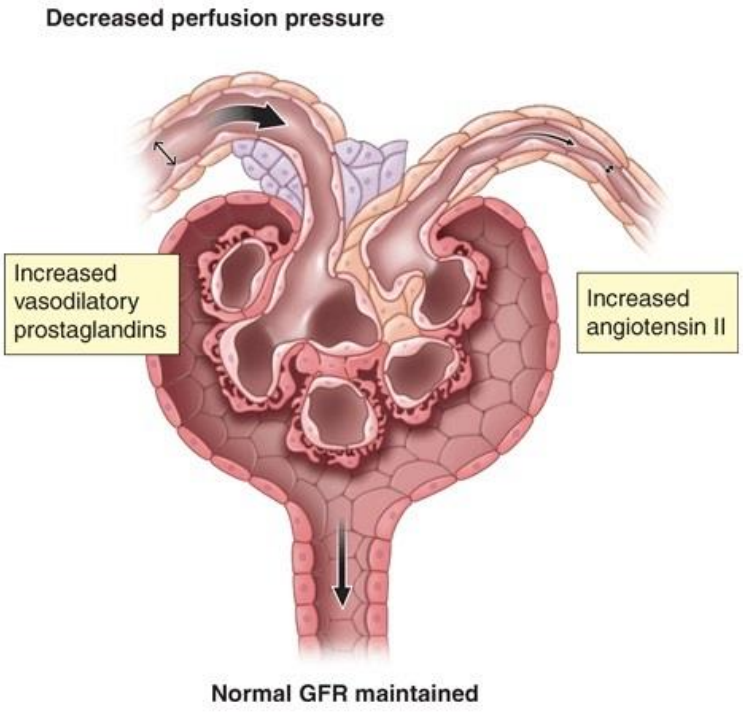


Fig-3 Renal auto regulation

If renal perfusion is decreases, vasodilatory prostaglandins dilates the afferent arterioles and angiotensin constricts the efferent arteriole, so glomerular perfusion pressure and glomerular filtration rate maintained

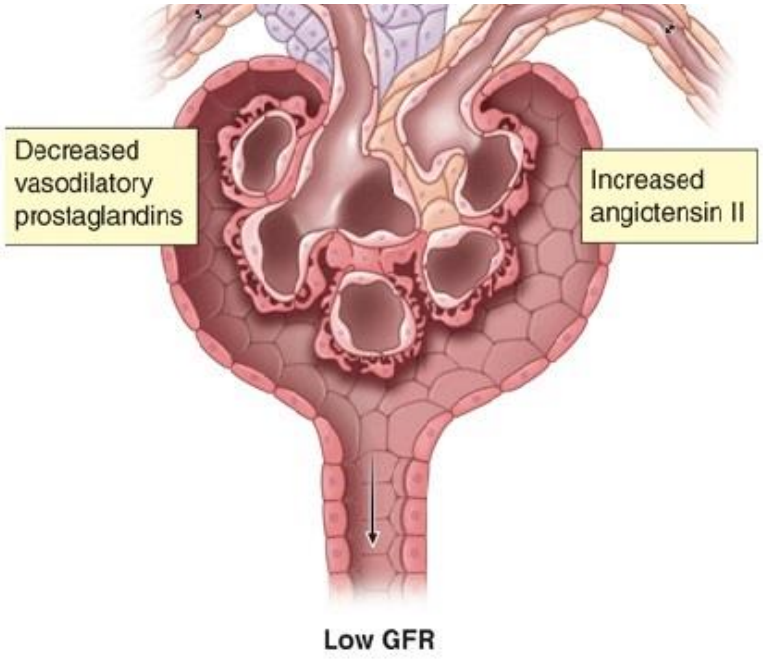


Fig-4 In the presence of NSAIDs this afferent arteriole vasodilatation by prostaglandins is affected, so there is decreased perfusion pressure

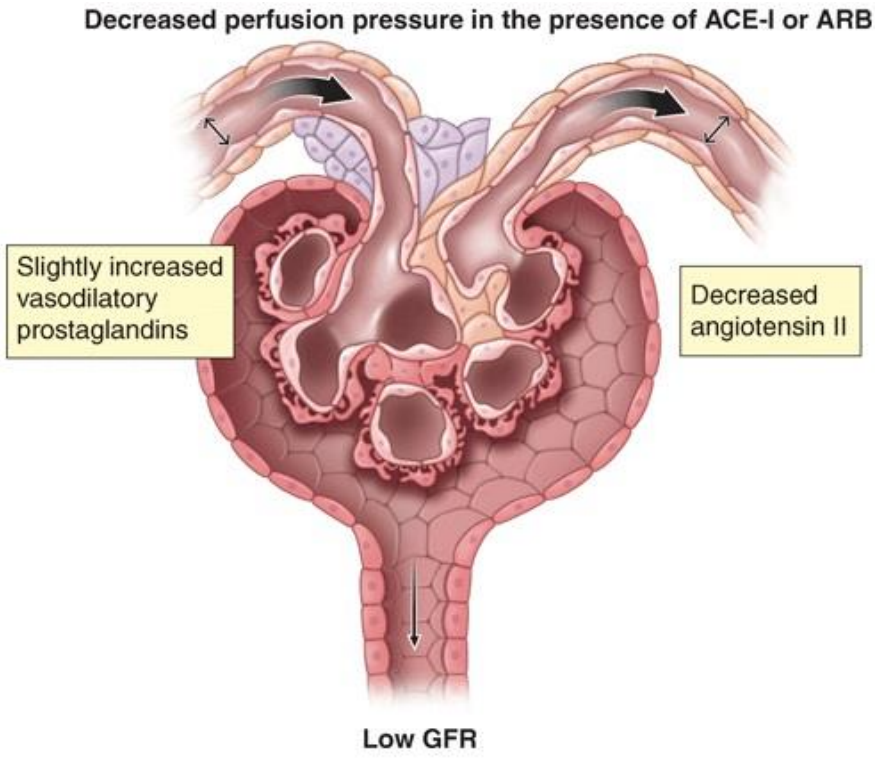


Fig-5 If ACE inhibitors given for patients with decreased perfusion pressure, there is no vasoconstriction of efferent arteriole, thereby decreases glomerular filtration rate[8].

In cirrhosis, due to splanchnic vasodilatation there is decrease in effective circulatory volume. So there is systemic vasoconstriction like that is seen in hypovolemic state. Triggering factors for AKI in cirrhotic patients are sepsis and diuretic over usage. Type I is severe form of AKI seen in cirrhosis, which is very difficult to manage and fails to recover even after maintenance of adequate intravascular volume. Type II is less severe form seen in cirrhosis with refractory ascites. The treatment of choice of both types of hepatorenal syndrome is liver transplantation[9].

INTRINSIC AKI

Most of the cases of the intrinsic AKI are due to progression of pre renal azotemia to acute tubular necrosis. This is also seen in sepsis, ischemia and nephrotoxic agents[9]. Basic pathophysiological mechanism in this type of AKI is inflammation and apoptosis.

NEPHROTOXIN ASOCIATED AKI

Because of relatively high percentage of blood supply, nephrotoxins reach kidney in high concentrations. Mostly nephrotoxins affect the renal tubule and epithelium but any part of the kidney can be affected by nephrotoxic substances. Hypoalbuminemia is associated with increased risk of AKI because there is increased fraction of unbound drug or nephrotoxins.

SEPSIS ASOCIATED AKI

More than half of the patients admitted with sepsis develop AKI even in the absence of hypotension. But some patients may also have associated hypotension. Renal tubular injury occurs in sepsis which leads to cellular debris and tubular casts. Systemic inflammatory state and interstitial edema also contribute to AKI. In sepsis there is an increased cytokine production, which leads to systemic vasodilatation and results in decreased renal perfusion and GFR[9].

ISCHEMIA ASSOCIATED AKI

As kidneys receive 20% of the cardiac output it is most susceptible to ischemia. Renal medulla is very much metabolically active, so it is susceptible to hypoxia mediated AKI[10]. Ischemia alone is not enough to cause AKI. When it is associated with chronic renal failure, septicemia, concurrent usage of nephrotoxic drugs, burns or pancreatitis it can lead on to AKI.

POST OPERATIVE AKI

This is a type of AKI seen after major surgeries with significant amount of blood loss during the procedure. Most common surgical procedures associated with AKI are vascular surgery, abdominal surgery, and cardio pulmonary bypass surgery. Risk of developing AKI is increased when there is a history of previous renal failure, elderly patients and during emergency procedure. Contrast agents used during diagnostic procedures are also associated with increased risk of AKI during post-operative period[10]. Prolonged duration of surgery and embolism during vascular surgery are all associated with increased risk of AKI.

BURNS AND PANCREATITIS

In pancreatitis there is accumulation of large amount of fluid in third space, which lead on to low perfusion to kidney. And as there is activation

of inflammation, it also causes AKI. If large volume of fluid accumulates in the peritoneal space, there is increased intra-abdominal pressure which causes compression of renal vein and AKI[10]. In burns, there is large amount of plasma leakage through exposed skin, thereby increasing risk of AKI.

CONTRAST AGENTS

Iodinated contrast agents used in CT angiogram and coronary angiogram are associated with increased risk of AKI. It is very unusual in patients with adequate hydration and normal GFR. Risk increases with diabetes and hypovolemic states. It is characterized by elevation of serum creatinine to more than 1.5mg/dl within 24 to 48 hours after contrast exposure[11]. Peak reaches after 3 to 5 days and return to normal in 1 week. Very rarely patients may develop severe renal failure; in those cases dialysis may be needed. Mostly patients will not develop acute tubular necrosis. This type of AKI develops due to direct toxicity of contrast agents; reactive oxygen species mediated injury or decreased blood supply to renal medulla due to occlusion of renal micro vessels[11]. Even high dose of gadolinium, oral sodium phosphate can cause renal injury.

ANTIBIOTICS

Antibiotics can cause AKI. Amphotericin B causes reflex vasoconstriction of renal vessels and direct damage to the tubules. Toxicity

is duration and time dependent. Amphotericin binds with tubular membrane and causes pores in it, through which cellular contents leak. Toxicity of this drug is characterized by low urinary concentration, increased frequency of micturition, and metabolic acidosis. Aminoglycoside antibiotics such as gentamycin and streptomycin cause renal injury by direct tubular toxicity. It is the most common pathological mechanism behind the renal failure in aminoglycoside use[12]. It causes non oliguric renal failure. Urine is typically hypo-osmolar in concentration. It may cause injury in normal plasma concentration also. Measurable quantity of drug reaches the proximal convoluted tubule cells and causes damage to them. It is associated with low serum magnesium concentration.

Vancomycin in high doses can cause renal injury. Acyclovir when used in dehydrated states precipitates in renal tubules and causes obstructive nephropathy. Renal tubular toxicity is also caused by cidofovir, pentamidine and foscarnet. Other drugs causing tubular damage are cisplatin and carboplatin which can be prevented by adequate hydration. Penicillin, cephalosporin, quinolones and rifampin cause interstitial nephritis. Cyclophosphamide and ifosfamide cause tubular damage and hemorrhagic cystitis. Gemcitabine, bevacizumab and mitomycin-c cause thrombotic micro angiopathy manifested by proteinuria and hypertension.

TOXIN INGESTION

Ethylene glycol causes direct tubule damage; it is used as automobile anti-freeze. Melanamine present in the certain food stuffs can cause renal stone and acute kidney injury. Consumption of Chinese herbs containing aristocholic acid causes Chinese herbs nephropathy and progressive renal fibrosis. Unidentified environmental toxins can cause chronic tubular interstitial nephritis.

ENDOGENOUS TOXIN

Whenever there is hemolysis or rhabdomyolysis, hemoglobin or myoglobin is released into systemic circulation respectively. These pigments deposit in the renal tubule and can cause pigment nephropathy. This can be prevented by alkalization of urine. Tumor lysis syndrome is seen in conditions like leukemia and lymphoma. After starting chemotherapy large amount of uric acid is released into circulation, which precipitates in the renal tubules causing renal injury. In multiple myeloma there is deposition of light chains in the renal tubules. These light chains can cause myeloma kidney. By causing vasoconstriction and volume depletion, hypercalcemia can cause renal tubular injury.

Differentiating prerenal and ATN by urine analysis

	Pre-renal	*ATN*
Urine Osmolarity (mOsm/L)	>500	<350
Urine Na (mmol/L)	<20	>40
Urine/plasma creatinine	>40	<20
Urine/plasma urea	>8	<3
Fractional Na excretion (%)	<1	>2

POST RENAL AKI

Post renal acute kidney injury occurs due to any obstruction from the renal pelvis to urethra. In post renal AKI there is increased pressure in the tract which interferes with glomerular filtration. Even if urine output is normal it does not rule out the urinary tract obstruction. Benign prostatic hypertrophy, prostate cancer, anti-cholinergic drugs, neurogenic bladder, blocked Foley's catheter, and urethral stricture are the most common causes of post renal AKI. USG abdomen and pelvis, CT abdomen and MRI abdomen are necessary to localize the site of obstruction.

COMPLICATIONS OF AKI

Excretion of sodium and potassium is decreased in AKI leading to volume overload, electrolyte imbalance such as hyperkalemia and

hyponatremia. Other metabolic abnormalities are hyperphosphatemia, hypermagnesemia and hypocalcemia. Oliguric patients have elevated creatinine and urea and these patients are at increased risk of complications. Acidification of urine is impaired in AKI leading to metabolic acidosis. Impaired excretion of nitrogenous substances cause uremic syndrome.

The increased intravascular volume seen in most of the AKI patients is due to impaired salt and water excretion. Clinical features of the AKI are elevated jugular venous pulse, crepitations in the lung bases, pleural effusion, ascites, facial puffiness, mild elevation of BP, recent increase in body weight and pulmonary edema. If blood pressure is very high we have to think of some other co-existing problems. Hypotonic solutions should be avoided in AKI patients because it may worsen hyponatremia[13].

The most important complication of AKI is hyperkalemia, as it is directly associated with increased mortality. Mostly this is seen in oliguric renal failure patients. Co-existing metabolic acidosis worsens the hyperkalemia, which causes efflux of potassium from the cells. If serum K^+ is less than 6Meq/L, it usually not associated with any symptoms. Severe hyperkalemia is mostly seen in conditions associated with massive destruction of cells like rhabdomyolysis, hemolysis and tumor lysis syndrome. Elevated serum potassium is associated with certain ECG

features such as reduced amplitude of P waves, PR interval prolongation, tall and tented T waves and sine wave pattern. It may result in bradycardia, complete heart block, ventricular tachycardia, ventricular fibrillation and asystole (diastolic arrest). Neuromuscular abnormalities associated with hyperkalemia are diminished deep tendon reflex, respiratory muscle weakness and weakness of limbs[13, 14]. Hypokalemia is very rarely seen in AKI except in non-oliguric ATN caused by drugs.

In AKI there is increased production of sulfuric acid and phosphoric acid, due to increased catabolism of proteins. These acids are usually excreted by kidneys. Impaired excretion of these acids leads to metabolic acidosis in AKI. Very severe acidosis can be seen if there is associated diabetic ketoacidosis, lactic acidosis and sepsis. Very rarely metabolic alkalosis may present in AKI due to over correction of acidosis or loss of hydrochloric acid due to severe vomiting.

Mild elevation of serum uric acid level may be seen in AKI, usually it is asymptomatic. If uric acid levels are high, urate nephropathy should be thought of. Over production of urate is differentiated from impaired excretion by measuring urinary urate and creatinine ratio. If the ratio is <1 it is due to impaired excretion and if the ratio is >1 it is due to overproduction.

AKI is associated with mild hyperphosphatemia. If serum phosphate level is very high, it may be due to massive destruction of cells, which is seen in hemolysis, tumor lysis syndrome and rhabdomyolysis. When calcium and phosphorus product is more than 70, it is associated with deposition of calcium phosphate in tissues. Asymptomatic hypocalcemia seen in AKI; it is due to the effect of acidosis on neuromuscular hyper excitability. It becomes symptomatic when acidosis is corrected with bicarbonate. Clinical manifestations of hypocalcemia are cramps, perioral numbness, tetany and convulsions. ECG features of hypocalcemia are QT prolongation and T wave changes[14]. Trousseau and chvostek signs positivity indicates latent tetany. A mild asymptomatic elevation of serum magnesium is also seen in AKI.

Hemodilution due to volume overload, impaired erythrocyte survival, decreased erythropoietin secretion, lysis of RBC all lead to anemia in AKI. Bleeding time is increased due to mild thrombocytopenia. Leukocytosis may present in AKI. Co-existent infection increases the mortality in AKI.

Cardiac complications seen in AKI are arrhythmia and pulmonary embolism. Myocardial contractility is decreased in AKI, due to metabolic acidosis, fluid overload, hyperkalemia and other electrolyte disturbances[15]. Mostly pulmonary embolism is due to prolonged immobilization. Upper

gastrointestinal bleeding can occur due to stress ulcer. Metabolic encephalopathy, uremic encephalopathy and thrombotic microangiopathy are causes of altered mental status seen in acute renal failure.

Malnutrition is one of the most dreaded complications of AKI. Various factors contributing to this are massive myolysis, decreased food intake, loss of nutrient during dialysis and decreased synthesis of muscle protein[16]. Patients with AKI may also have pericarditis and tamponade. GIT complications are nausea, vomiting, anorexia and paralytic ileus.

Neurological manifestations of AKI are lethargy, psychosis, myoclonus, confusion, asterixis and coma. Uremic manifestations of AKI are due to aromatic amines, guanidine compounds and urea.

Diuretic over usage during recovery may cause volume depletion and further aggravates the kidney injury. If fluid intake is not adequate in this period, hypernatremia can occur. If urine output is more than 400 ml/day it is called non-oliguric renal failure and less than 400ml/day it is called oliguric renal failure. If urine output is less than 100ml/day it is called as anuria[17]. Less urine output indicates more severe renal injury.

COURSE OF AKI

There are 3 phases in AKI (1) Initiation phase

(2) Maintenance phase

(3) Recovery phase

Initiation phase is a reversible period extending from exposure to the toxin or initiating event to the onset of kidney injury but not fully established. This is followed by maintenance period. In this phase the kidney parenchyma is fully injured and glomerular filtration lowers to the approximately around 10ml/min. In this phase patient is mostly oliguric. This phase will last for up to 2 weeks[17]. Very rarely this may be prolonged for months together. During Recovery phase there is increase in urine output and returning of biochemical abnormalities to base line.

DIAGNOSIS

While evaluating the patient with elevated renal parameters it is essential to differentiate AKI from CKD. Hypertension, anemia, hyperparathyroidism, evidence of renal osteodystrophy and bilateral contracted kidneys in ultra-sonogram are suggestive of chronic kidney disease. Anemia is also present in long standing acute kidney injury. Normal or increased sized kidneys are seen in CKD with polycystic kidney

disease, diabetes, amyloidosis and HIV nephropathy. Once diagnosis of AKI is confirmed, we have to differentiate it into prerenal, intrinsic and post renal AKI. For this detailed history and clinical examination should be done.

INVESTIGATION

- Urine analysis: albumin, sugar, deposits, casts, specific gravity, eosinophil.
- Complete hemogram with peripheral smear
- Blood: serum creatinine, blood urea, serum electrolytes.
- Autoantibody: ANA, ANCA, Anti glomerular basement membrane.
- ASO titre, anti-DNAse titre.
- Serum electrophoresis.
- Ultra sonogram of abdomen.
- CT abdomen &Renal biopsy

MANAGEMENT OF AKI

Prime important in the management of AKI is the treatment of the underlying precipitating event. Management consists of monitoring of vital parameters, avoiding and stopping nephrotoxic drugs, fluid and electrolyte correction and adjustment of dose of drugs according to glomerular

filtration rate. Usually kidneys recover from the injury with this supportive care. Rarely some patients require dialysis for some period.

Renal replacement therapy in the form of dialysis is also a supportive therapy. It doesn't improve the kidney recovery.

Indications for renal replacement therapy are

1) Hyperkalaemia
2) Refractory acidosis
3) Refractory volume overload
4) Uremic symptoms.

OUTCOME

Mortality is very high in intrinsic AKI as compared with other two forms. Mortality rate varies depending upon the etiology. 30% in toxin induced AKI, 60 to 70% in sepsis induced and 15% in gynecological causes[18].

Factors associated with poor prognosis are

1) Serum creatinine more than 3 mg/dl
2) Male patients
3) Oliguric AKI
4) Old age

CHRONIC KIDNEY DISEASE

Chronic kidney disease is emerging as a major health related issue worldwide. Developing countries like India are not able to manage these patients because of increasing cost. Incidence and prevalence of CKD is increasing because of the increased survival and improved quality of treatment. The term chronic renal failure corresponds to CKD stages 3-5, applies to the processes of irreversible reduction in nephron number. End stage renal disease represents the stage in which survival is not possible, unless the uremic toxins are removed by appropriate renal replacement therapy. This syndrome is caused by accumulation of toxins, fluids and electrolytes that are normally excreted by kidneys.

Most common causes of ESRD are diabetes, hypertension, polycystic kidney disease and glomerulonephritis. These together contribute to more than 90% of the cases of ESRD. Other causes for CKD include interstitial nephritis and HIV[19]. Nephropathy due to systemic hypertension is the most common cause for end stage renal disease in elderly patients. Nephrosclerosis from vascular disease process correlates with coronary and cerebrovascular disease.

Because of decreased mortality related to atherosclerotic coronary complications, greater segment of the population manifests the renal counter part of generalized vascular disease. In early stages of CKD,

patients usually will die of cardiovascular and cerebrovascular complications before they progress to ESRD. Renal disease progression varies from person to person, so this leads to genetic research to identify the inheritable component. A number of genetic loci that are contributing to the development of kidney disease have been identified.

Chronic kidney disease is divided into five stages based on the estimated glomerular filtration rate (GFR). In stage 1and stage 2 the GFR is normal or near normal, so based on the structural or functional defect these two are differentiated.

DEFINITION OF CHRONIC KIDNEY DISEASE

The National Kidney Foundation [Kidney Disease Outcomes Quality Initiative (KDOQI)] has proposed a definition and classification scheme of CKD. The National kidney foundation guidelines define CKD on the basis of kidney damage and/or reduced renal function. Kidney damage may be confirmed through a variety of methods including renal imaging, abnormalities in the serum or urine biochemistry and histological evidence. Albuminuria is the most frequent early indicator of kidney damage.

CRITERIA:

1. Structural or functional abnormality of the kidney for more than 3 months, with or without decreased urine output, manifested by

- Pathological abnormalities
- Markers of kidney damage
    i. Urinary abnormalities (proteinuria).
    ii. Blood biochemical abnormalities.
    iii. Imaging abnormalities.

2. GFR <60 ml/min/1.73m^2 BSA for >3 months with or without kidney damage.

RISK FACTORS FOR CKD

Established risk factors:

- Age
- Gender
- Race
- Diabetes mellitus
- High blood pressure
- Proteinuria
- Atherosclerosis
- Family history of kidney disease
- Reduced nephron number at birth
- Obesity

- Metabolic syndrome
- Family history of kidney disease
- Smoking
- Exposure to nephrotoxins
- Dyslipidaemia
- Recurrent urinary tract infection

Emerging risk factors:

- Elevated plasma homocysteine level
- Oxidative stress
- Prothrombotic factors (e.g. Plasminogen activator protein)
- Anaemia

STAGES OF CHRONIC KIDNEY DISEASE

Kidney disease outcome quality initiative (NKF-KDOQI) staging system: Importances of this staging are[20, 21]

1. It shifts the focus from GFR as the sole criteria for defining chronic kidney disease to the identification of markers of early kidney damage including proteinuria and abnormal urinary sediment.

2. The concept of CKD with normal glomerular filtration rate, but with markers of kidney damage like persistent proteinuria is providing guidelines for optimal treatment at early stage.

This system of staging helps us to plan for further treatment and also helps in predicting the outcomes. Thus there is a need for early detection and treatment.

STAGE	**DESCRIPTION**	**GFR (ml/min/1.73m^2)**	**ACTION**
1	Kidney damage with normal GFR	>90	Diagnosis and treatment of comorbid condition, slow progression, CVD risk reduction.
2	Kidney damage with mild reduction of GFR	60-89	Estimating progression.
3	Moderate reduction of GFR	30-59	Evaluate and treat complication.
4	Severe reduction of GFR	15-29	Preparation of renal replacement therapy.
5	ESRD	<15	Renal replacement therapy

CAUSES OF CHRONIC KIDNEY DISEASE

1. Diabetic glomerulosclerosis
2. Hypertensive Nephrosclerosis.
3. Glomerular diseases:
    - Glomerulonephritis
    - Amyloidosis, light chain disease.
    - Systemic lupus erythematosus.
    - Wegener's granulomatosis.
4. Tubulointerstitial diseases:
    - Reflux nephropathy (chronic pyelonephritis).
    - Analgesic nephropathy.
    - Obstructive nephropathy (stones, benign prostatic hypertrophy).
    - Myeloma kidney.
5. Vascular diseases:
    - Scleroderma.
    - Vasculitis.
    - Reno vascular renal failure
    - Atheroembolic renal disease.
6. Cystic diseases:
    - ADPKD.
    - Medullary cystic kidney disease.

There is a difference between the etiologies of CKD in India when compared to world-wide incidence. For example, in North America the commonest cause for CKD is diabetic nephropathy and the next being hypertensive glomerulosclerosis. But in India although large scale data are unavailable, glomerulonephritis is the leading cause for CKD over diabetes and hypertension.

In most of the patients while diagnosing CKD, there is an associated systemic hypertension. If there is no identifiable cause for glomerular disease or tubular pathology, the etiology is often attributed to systemic hypertension. But such patients without identifiable etiological factors are considered in the following categories.

1) Patient with silent primary glomerulopathy, like focal segmental glomerulosclerosis without overt nephrotic or nephritic manifestations of glomerular disease.
2) Patients with chronic renal ischemia attributed to systemic vascular disease involving large and small vessels, cardiac and cerebral pathology. Here systemic hypertension is considered to be the renal correlate of systemic vascular disease.

PATHOPHYSIOLOGY OF CKD

It involves two broad sets of mechanisms

1. According to the mechanisms that are specific to the underlying etiology that initiate the kidney damage. (e.g. Genetic abnormalities in the development of kidney, deposition of immune complexes and inflammatory mediators as in glomerulonephritis or exposure of toxins in diseases of renal tubules and interstitium).

2. Progressive mechanisms involving hyper filtration and hypertrophy of the remaining viable nephrons that are common consequence following reduction of renal mass, irrespective of the underlying etiology. These adaptive responses to reduction in nephron number are mediated by a number of vasoactive hormones, cytokines and growth factors. Renin aldosterone system is responsible for hyperfiltration and subsequent hypertrophy and sclerosis.

The increased intra-renal renin activity contributes to both initial inciting event and also to the progressive mechanisms, finally leading on to the glomerular sclerosis, renal failure and uremic syndrome.

PATHOPHYSIOLOGY OF UREMIC SYNDROME

The pathophysiology behind the uremic syndrome can be classified into

1) Due to the accumulation of toxins that are normally excreted via the kidneys.
2) Due to impairment of fluid and electrolyte homeostasis and hormone regulation.
3) Progressive systemic inflammation and its consequences

Various excretory products accumulating in renal dysfunction are nitrogenous and non-nitrogenous products such as urates, products of nucleic acid metabolism, phenols, guanido compounds, hippurates, indoles, middle molecules, etc. Accumulation of these waste products leads to anemia, metabolic abnormalities of carbohydrate, protein and fat and malnutrition resulting in a clinical syndrome which is characteristic feature of end stage renal disease. There is alteration of metabolism of many hormones like insulin, glucagon, PTH and vitamin-D due to increased renal excretion, decreased degradation and abnormal regulation.

SUMMARY OF PATHOPHYSIOLOGY OF CKD

Vasoactive molecules, cytokines, growth factors, renin angiotensin axis

↓

Glomerular hyperperfusion, hypertension, hyperfiltration

↓

Glomerular hypertrophy and sclerosis

↓

Reduced renal mass and function.

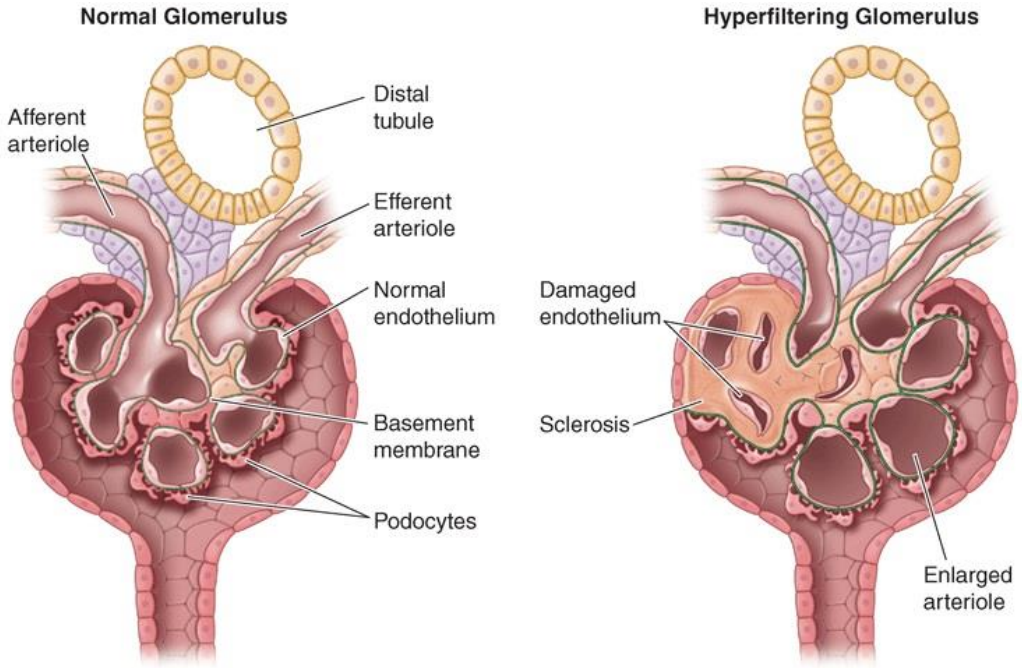


Fig-6 Due to chronic nephron loss some of the viable nephrons become hypertrophied and enlarges[8, 9].

FACTORS INFLUENCING RENAL PROGRESSION

There are some factors affecting the progression of renal disease. The rate of disease progression can be modified by modifying these risk factors. It includes:

1. Hypertension.
2. Diabetes.
3. Hyperlipidaemia.
4. Abnormal calcium-phosphorus homoeostasis.
5. Genetic factors.
6. Cigarette smoking.
7. Renin-angiotensin system activation.
8. Excessive dietary protein.
9. Obesity.
10. Prematurity/low birth weight.

CLINICAL PRESENATION

Most of the patients are asymptomatic in the early stages of chronic kidney disease; mostly they do not come to medical attention until most of the kidney function is compromised by the disease process. Any organ system can be affected by the kidney disease. Anemia, proteinuria and hypertension are the most common manifestations present in the most of

the patients. Clinical presentation depends upon the systems involved. These include:

1) Disorders of fluid, electrolyte and acid-base homeostasis
2) Disorders of calcium and phosphate metabolism
3) Disorders of cardiovascular system
4) Haematological abnormalities
5) Neuro-muscular abnormalities
6) Gastro-intestinal and nutritional abnormalities
7) Endocrine-metabolic disturbances
8) Dermatological abnormalities

ELECTROLYTE AND ACID-BASE DISORDERS

SODIUM AND WATER HOMEOSTASIS

In patients with stable CKD, there is a clinically insignificant increase in total body water and sodium content. In most of the CKD patients daily intake of sodium exceeds its urinary excretion leading to sodium retention and extracellular volume expansion. This is also one of the contributing factors for development of hypertension. Hyponatremia is very rarely seen in CKD patients; even if present it will respond to water restriction.

POTASSIUM HOMEOSTASIS

Hyperkalemia in CKD may be due to the following mechanisms:

A. Increased dietary potassium intake

B. Protein catabolism

C. Hemolysis

D. Transfusion of stored blood

E. Metabolic acidosis.

Hypokalemia is not common in CKD. It may occur in markedly reduced dietary intake, excessive diuretic therapy and gastro intestinal losses.

Metabolic acidosis:

It is a common metabolic abnormality seen in ESRD patients. The combination of hyperchloremic metabolic acidosis and hyperkalemia is often present. In early stages of CKD non anionic gap metabolic acidosis is present, but in later stages anionic gap metabolic acidosis ensues. Renal ammonia production is increased during treatment of hyperkalemia and also renal production of bicarbonate is increased, thereby improving the metabolic acidosis.

BONE MANIFESTATIONS OF CKD

The two main types of bone disease in chronic kidney disease are adynamic bone disease and osteitis fibrosa. Low bone turnover leads to adynamic bone disease and osteomalacia. It is most commonly seen in diabetes and elderly individuals. Adynamic bone disease is characterized by decreased mineralization and bone volume resulting in fracture and pain. It is also associated with vascular and cardiac calcification. Osteomalacia is caused by metabolic acidosis, vitamin D deficiency and aluminium deposition that are present in the alkali. Secondary hyperparathyroidism that is seen in CKD is the main reason for high bone turn over. This high bone turnover causes osteitis fibrosa cystica. This is characterized by fragility, brown tumors and compression syndromes. Renal osteodystrophy results from secondary hyperparathyroidism.

GASTROINTESTINAL MANIFESTATIONS

Gastritis, peptic ulcer disease and mucosal ulcerations can occur in any part of GI tract resulting in abdominal pain, nausea, vomiting and GI bleeding. These patients are prone for constipation which can be worsened by calcium and iron supplements. Protein energy malnutrition is common in advanced stages of CKD. It is due to low protein diet and increased

catabolism of proteins. Metabolic acidosis and activation of inflammatory cytokines promote protein catabolism. Every patient should be assessed for malnutrition from stage 3 of CKD.

NEUROMUSCULAR MANIFESTATIONS

Central nervous system, peripheral and autonomic neuropathy as well as abnormalities in the muscle structure and function are recognized complications of CKD. Nitrogenous metabolites and middle molecules that are accumulating in CKD contribute to the pathophysiology of neuromuscular abnormalities. In the early stages of CKD, patients present with disturbances in the memory, sleep and concentration. Neuromuscular irritability including hiccups, cramps and fasciculation or twitching of muscles are seen in later stages. Asterixis, myoclonus, seizures and coma may occur in advanced untreated cases due to uremic encephalopathy[21, 22].

Presence of peripheral neuropathy without any other cause is one of the indications for renal replacement therapy; it usually occurs from stage 4 of CKD. Sensory nerves more involved than the motor. It presents as distal symmetric polyneuropathy.

ENDOCRINE & METABOLIC MANIFESTATIONS

Metabolism of glucose is impaired in chronic kidney disease. As insulin excretion by the kidneys is impaired, there is elevation of plasma

insulin level. As hypoglycemic episodes are more common in CKD, doses of insulin and oral hypoglycemic agents should be reduced. In women with CKD, estrogen levels are low. Menstrual abnormalities and infertility are common. Pregnancy may hasten the progression of the disease. Spontaneous abortions and miscarriages are common. Sexual dysfunction and oligospermia are common in men with CKD.

DERMATOLOGIC MANIFESTATIONS

Most common and devastating complication of chronic kidney disease is pruritus. Hyperpigmentation of the skin is also one of the dermatologic complications of the CKD. Progressive subcutaneous induration of arms and legs occurs in CKD patient after exposing them to gadolinium contrast. It is called nephrogenic fibrosing dermopathy.

HYPERTENSION AND CHRONIC KIDNEY DISEASE

Hypertension is almost present in all the CKD patients and often the first manifestation of the disease. More than 90% of patients with CKD experience hypertension during the course of the disease. Uncontrolled hypertension accelerates the rate of progression of the renal disease. Clinical trials and epidemiologic studies indicate that hypertension is a major risk factor for CKD. Hypertension contributes to the development of

cardiovascular disease, the leading cause of morbidity and mortality in CKD patients.

Hypertension in CKD patients is mainly the result of an increased extracellular volume and a decreased excretion of sodium. Another mechanism for hypertension in CKD patients is the activation of renin – angiotensin – aldosterone system (RAAS) and the sympathetic nervous system. Vasoconstrictive action of the angiotensin and salt retaining property of the aldosterone are responsible for hypertension seen in CKD patients. Serum uric acid level is also elevated in CKD patients thus contributing to vascular damage and hypertension.

Multiple Risk Factor Trial (MRFIT) has established a strong correlation between hypertension and rate of decrease in kidney function. National Health and Nutrition Evaluation Survey (NHANES) III suggests that adequate control of BP is achieved in only eleven percent of the patients. Causes for uncontrolled hypertension in chronic kidney disease patients are

1) Age more than 60 years
2) Presence of albuminuria
3) Associated other diseases like coronary heart disease, cerebrovascular accident and diabetes.

Documentation and serial monitoring of blood pressure in every CKD is vital, because this strongly correlates with disease progression and cardiovascular event. Treatment of high BP in CKD should include specification of target blood pressure levels, nonpharmcologic therapy and specific anti-hypertensive agents for the prevention of progression of kidney disease and cardiovascular morbidity. Antihypertensive treatment reduces albuminuria and reduces its progression even in normotensive diabetic patients. Degree of blood pressure control appears to be an important factor in the rate of progression of CKD.

Based on the kidney disease improving global outcomes (KDIGO) the following were practiced in the management of hypertension in CKD.

1. In both diabetic and non-diabetic CKD patients with BP more than 140 mm Hg systolic and 90 mm Hg diastolic should be treated with anti-hypertensive drugs.

2. The target BP to be achieved was based on urine albumin excretion rate.
    - For patients with urine albumin excretion of less than 30mg per 24 hours the BP should be maintained at <140mm Hg systolic and <90 mm Hg diastolic.

- For patients with urine albumin excretion of more than 30 mg per 24 hours the BP should be maintained at <130 mm Hg systolic and <80 mm Hg diastolic.

3. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) can be used to achieve the target BP.

4. Individualize BP target and agents according to age, coexistent cardiovascular disease and other co-morbid illness and tolerance to the treatment.

5. The combinations of ACE inhibitors with ARBs are not recommended.

ANEMIA AND CHRONIC KIDNEY DISEASE

Anemia is one of the most common problems in chronic kidney disease patients. The cause for anemia in CKD is multifactorial. Usually it is normochromic due to erythropoietin deficiency and other factors like iron deficiency also contributes a major proportion. Anemia is a multifactorial risk factor for the progression of CKD to end stage renal disease (ESRD) which reduces the quality of life and associated with significant morbidity and mortality.

Anaemia in diabetic patients has peculiar features as early onset and more severe in magnitude. Severity of the anaemia reflects the severity of the disease. Absolute level of haemoglobin that defines anaemia in CKD has been determined by national kidney foundation's kidney disease outcome quality initiative guidelines as a level of less than 12 gm/dl for men, postmenopausal women and 11 gm/dl in premenopausal women.

In general, anaemia becomes more frequent as renal function declines, becoming almost universal in ESRD. Studies have demonstrated correlation of anaemia with progression of renal failure. A randomized cohort study RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) reports that each 1g/dl decrease in hemoglobin concentration from baseline is associated with an 11% increase in the risk of developing renal failure. Moderate to severe anaemia, (hematocrit less than 33%) is common only when GFR is less than 30ml/min in women and 20ml/min in men. Erythropoietin deficiency along with absolute or functional deficiency of iron, accounts for nearly 90% cases of anaemia. Anaemia is also a risk factor for the progression of CKD. Several small studies indicate that treatment of anaemia may slow the progression of CKD. Anemia in CKD is usually normocytic normochromic anemia. If microcytosis is present, then iron deficiency, thalassemia and myelodysplasia should be considered.

ETILOGY OF ANEMIA IN CKD

BASIC ETIOLOGY

1) Erythropoietin deficiency.
2) Iron deficiency (absolute/functional).
3) Decreased RBC survival.
4) Reduced dietary intake and absorption.
5) Bleeding diathesis.
6) Urinary loss of transferring as a part of proteinuria leading to impaired iron transport.

CONTRIBUTORY FACTORS:

a) Uremic toxins.
b) Immunosuppressive drugs.
c) Aluminium toxicity.
d) Secondary hyperparathyroidism and bone marrow fibrosis.
e) Folate and vitamin B12 deficiency.
f) Associated HIV/HCV infections.
g) Chronic inflammation and release of inflammatory cytokines.
h) Haemoglobinopathy.
i) Co-morbid conditions like hypo/hyperthyroidism, pregnancy, auto-immune diseases.

Anaemia and its direct consequence, reduced oxygen delivery and utility may have detrimental effects in patients with CKD. Worsening of anaemia could potentially accelerate the progression of kidney disease. Anaemia has a direct effect on cardiovascular system increasing the morbidity and mortality in CKD patients. Anaemia plays an important role in the development of congestive cardiac failure and left ventricular hypertrophy. Reduced oxygen carrying capacity consequent to anaemia in CKD results in tissue hypoxia which in turn aggravating the uremic symptoms. It also produces a state of abnormal haemostasis. Anaemia plays an important role in platelet dysfunction. The phagocytic activity of the granulocytes may be reduced. Cell-mediated immunity is depressed resulting in increased incidence of infections.

EVALUATION OF ANEMIA IN CKD

Because the diagnosis of erythropoietin deficiency is one of the exclusion, the evaluation should focus on excluding the other causes of anaemia with an appropriate history, examination and laboratory testing.

- Haemoglobin
- Complete blood count
- Red blood cell indices,

- Faecal blood testing and upper gastro duodenoscopy should be performed.
- Iron profile including serum Ferritin and transferrin saturation should be done to rule out iron deficiency.

If microcytosis is present then thalassemia, iron deficiency and myelodysplasia should be considered. With macrocytosis, folic acid and vitamin B12 deficiency must be excluded. Echinocytes or burr cells in peripheral smear are characteristic of CKD.

TREATMENT OF ANEMIA

Based on National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, the target haemoglobin to be achieved is 12 g/dl for both men and women regardless of stage of CKD. Patients with haemoglobin levels less than 11 g/dl are candidates for treatment. In adult CKD patients with anaemia, not on iron or erythropoietin therapy a trial of intravenous iron therapy is suggested. Erythropoietin therapy is not indicated in adult CKD patients with Hb concentration of more than 10 g/dl. And in patients with less than 10 g/dl the decision to start erythropoietin therapy should be individualized based on the rate of fall of hemoglobin, prior response to iron therapy, transfusion related risks and the risk related to erythropoietin therapy.

CALCIUM AND PHOSPHATE METABOLISM IN CKD

The main complication of abnormality in the calcium and phosphorus metabolism in CKD patients is calcium deposition in the vascular bed. As the kidneys play a major role in the calcium and phosphorous metabolism, they are essential to maintain the calcium and phosphorous in appropriate level. These abnormalities do not occur unless the GFR is reduced to 60ml/min. If the GFR reduced to 30ml/min, calcium and phosphorous abnormality will present in almost all patients. Commonly seen metabolic abnormalities include hyperphosphatemia, hypocalcemia and abnormal vitamin D metabolism.

Normal serum calcium and phosphorous levels are maintained by

1) Parathyroid hormone
2) 1, 25 dihydroxycholecalciferol.

These hormones act on three primary target organs: bone, kidney and intestine to maintain serum calcium and phosphorus.

Secondary hyperparathyroidism leads to metabolic abnormalities of calcium and phosphorous in the following ways.

- Reduced phosphate excretion due to declining GFR and phosphate retention.

- Retained phosphate stimulates parathyroid resulting in hyperparathyroidism and hyperplasia of the glands.
- Hypocalcaemia due to reduced calcitriol and phosphate retention also stimulates parathyroid resulting in hyperparathyroidism.

CHRONIC KIDNEY DISEASE-MINERAL BONE DISORDER

It is defined as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of Phosphorus, calcium, PTH and vitamin D metabolism.
- Abnormalities in bone turn over, mineralization, volume, growth or strength.
- Vascular and other soft tissue calcification.

CARDIO-VASCULAR EFFECTS OF CKD

The most common cause of mortality in chronic kidney disease is due to cardiovascular disease. There is 30 times higher mortality in ESRD patients when compared to age and sex matched general population. Cardiovascular mortality is higher in those patients with dialysis than patients without dialysis. Cardiovascular events start in early stages of kidney disease, so most of the patients die of cardiovascular mortality before reaching ESRD.

So management should begin in the early stage of the disease to prevent cardiovascular mortality.

The following conditions form the major part of the cardiovascular complications of CKD,

1) Cardiomyopathy
2) Ischemic heart disease
3) Left ventricular hypertrophy
4) Cardiac failure

CVS risk is increased in CKD due to the vascular calcification. Most of the vascular calcification in CKD is due to dystrophic calcification. Aortic valve is affected more commonly than mitral valve. The Valvular calcification and atherosclerosis cause significant stenosis of the coronary artery.

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE IN CKD

Patients with CKD are more likely to develop cardiovascular disease related mortality because of accelerated atherosclerosis. In addition these patients present with atypical symptoms, which leads to delay in diagnosis and affects the outcome. Risk factors for cardiovascular disease are.

TRADITIONAL RISK FACTORS

- Male gender
- Smoker
- Dyslipidaemias
- Hypertension
- Left ventricular hypertrophy
- Diabetes mellitus
- Older age
- Physical inactivity

CKD RELATED RISK FACTORS

- Hypertension
- Sodium retention
- Angiotensin II
- Generalised inflammation
- Myocarditis, pericarditis
- Anaemia
- Proteinuria
- Hypervolemia
- Elevated calcium-phosphate product
- Hyperphosphatemia

- Hyperparathyroidism
- Genetic factors

EMERGING RISK FACTORS

- Insulin resistance
- Hyper homocysteinemia
- Lipoprotein.
- Inflammation.

Myocardial infarction is responsible for 30 to 50 percent of deaths in CKD patients. Myocardial ischemia tolerance is greatly reduced in CKD, even in the absence of associated atherosclerotic changes.

85% of the patients on dialysis already have left ventricular disease. Microvascular disease in the coronary circulation is also more common in CKD patients. Intramyocardial arterial wall thickening is present in the absence of associated hypertension and it interferes with perfusion of myocardium. Besides the anticipated accelerated atherosclerosis of aorta and peripheral arteries, calcification of the arterial media especially in the aorta lead on to aortic stiffness which is an independent risk factor for cardiovascular mortality. CKD is an inflammatory state which causes elevation of acute phase reactants like CRP and other inflammatory cytokines. In the presence of inflammation, vascular occlusive disease

process is accelerated, that too in the milieu of hyperphosphatemia leads to vascular calcification. So in every CKD patient we have to evaluate cardiovascular status.

HEART FAILURE

In more than 40 percent of patients there is a history suggestive of heart failure symptoms while starting dialysis; which is a significant factor for morbidity and mortality. Female sex, age, diabetes, atherosclerosis, structural cardiac abnormalities and pericarditis were associated with increased risk of heart failure in CKD patients. Patients those who are having left ventricular hypertrophy are associated with diastolic dysfunction. In uremia there is increased stiffness of left ventricle, so these patients will have diastolic dysfunction. There is also worsening of cardiac dysfunction in ESRD.

LEFT VENTRICULAR HYPERTROPHY

- It is an adaptive response occurring due to increased demand for myocardial work.
- Becomes maladaptive due to the imbalance between energy expenditure and production, resulting in chronic energy deficient state and cardiac myocyte death.

- In CKD, there is combined pressure and volume overload due to Left Ventricular (LV) hypertrophy.
- Pressure overload is due to sustained LV afterload because of hypertension, arteriosclerosis and aortic stenosis.
- Volume overload is due to increased extracellular volume, anaemia and arterio-venous fistula.

MANAGEMENT

VOLUME OVERLOAD

Because of risk of pulmonary edema, hypervolemia is life threatening in oliguric or anuric renal failure. Risk of pulmonary edema is very high if there is any previous lung disease. Fluids and salt should be restricted and diuretics may be useful. But increasing urine output does not alter the natural disease progression. In very severe volume overload, i.v bolus diuretics may be useful. If there is no response with bolus, we should stop diuretics. Sometimes low dose of dopamine may increase urine output.

ELECTROLYTE AND ACID-BASE ABNORMALITIES

No need to treat metabolic acidosis unless PH is less than 7.2 and serum bicarbonate <15mmol/L. Severe acidosis can be treated with oral or i.v sodium bicarbonate. Overcorrection of metabolic acidosis should be avoided, as this lead on to hypocalcemia, hypokalemia and metabolic

alkalosis. Hyperphosphatemia that is commonly seen in acute kidney injury can be treated with phosphate binders like sevelamer, calcium carbonate and aluminium hydroxide. Hypocalcemia that is seen in AKI does not require any treatment, unless patient is symptomatic.

ANEMIA

The anemia seen in AKI is usually not improved by erythropoiesis stimulating agents, because presence of bone marrow resistance and delayed onset of action. Bleeding seen in uremia may respond to desmopressin or estrogens. Sometimes dialysis may be required in uremic bleeding if uremia is severe or long standing. GI prophylaxis with PPI or H_2 blockers is required. Venous thromboembolism prophylaxis is dose adjusted based on GFR. As factor Xa inhibitors and low molecular weight heparin have unpredicted response, they should be avoided in acute renal failure.

DIALYSIS

Various methods of dialysis available are (1) Peritoneal dialysis

(2) Hemodialysis

(3) Hemofiltration

PERITONEAL DIALYSIS

Peritoneal dialysis uses the patient's peritoneum as semipermeable membrane. Dialysate is instilled into the abdominal cavity. Initially it was used in clinically unstable patients. With the invention of continuous hemodialysis it is very rarely used for AKI. Now-a-days most common indication for peritoneal dialysis is ESRD.

Two methods that are commonly used in peritoneal dialysis are

1) Manual method
2) Automated method

- In manual exchange also called as continuous ambulatory peritoneal dialysis (CAPD) patient has to introduce the dialysate into the peritoneal cavity for a particular time period. After the specific time period the dialysate is drained and replaced with another volume of peritoneal fluid for dwell.
- In automated method also called continuous cycling peritoneal dialysis (CCPD), usually performed at night where machine instills the dialysate into the peritoneal cavity at night as patient sleeps. Final fluid is kept in the abdomen for continuous solute exchange.

PRESCRIPTION OF PERITONEAL DIALYSIS:

Choice between the two methods depends upon patient preference and characteristics of peritoneum. Following parameters must be mentioned in the prescription-

- Volume of fluid- usually between 2-3 litres
- Dwelling time
- Concentration of dextrose- 1.5%, 2.5%, and 4.25%; higher concentration is needed to provide greater amount of fluid removal. But one of the main problems with high concentration solutions is absorption into circulation and worsening of the diabetes. Icodextrin, a glucose polymer can be used instead of dextrose, because it is poorly absorbed.

Peritoneal dialysis is less effective than haemodialysis in clearing of solute. If used in large volume and frequent exchanges it may approximate other renal replacement therapies. Residual renal function is very important in peritoneal dialysis patients.

COMPLICATIONS

- Peritonitis- patient usually presents with diffuse abdominal pain and colour changes in the dialysate. If peritonitis is suspected, sample should be sent for culture and sensitivity, cell count and gram

staining. Total count of >100cells/cumm, with > 50% polymorphs supports the diagnosis of peritonitis. Empirical antibiotic therapy should be started with first generation cephalosporin (cefazolin or cephalothin) and ceftazidime. Dose is 15-20mg/kg in each of these drugs. Once culture results are obtained, then antibiotics are changed according to that. If multiple organisms are present intestinal perforation should be thought of.

- Tunnel or exit site infections- patient may present with erythema, tenderness, and purulent discharge. Treatment with oral cephalosporin or oral fluroquinolone is needed.
- Outflow failure- it may be due to kinking of the catheter, plugging of the catheter with fibrin or constipation. Mostly it is managed conservatively with relieving of constipation and instilling the dialysate with heparin in the dose of 500units/L.
- Sclerosing encapsulating peritonitis- it is a one of the long term complication of the peritoneal dialysis. Peritoneum becomes thickened and encircles the small intestine and causes intestinal obstruction. It is mostly managed with bowel rest and if not resolved surgical lysis of adhesions.
- Hyperglycaemia, hyperlipidaemia and hypokalaemia.

HEMODIALYSIS

Most common form of renal replacement therapy employed in most of the renal injury situations.

- Intermittent hemodialysis runs typically 2-4 hours per session and weekly three times.
- Continuous renal replacement therapy (CRRT) - is used when patient hemodynamic status is unstable. Rate of blood flow is slow in this method, so anticoagulation is needed.
- Sustained low efficiency dialysis is a hybrid variety of intermittent hemodialysis and continuous renal replacement therapy; usually done for 8 to hours per day. So patient can engage in other investigations, procedures and ambulation.

PRESCRIPTION

Intermittent hemodialysis typically runs for 3 to 4 hours. In the chronic setting weekly three times is enough. In acute setting adequacy of dialysis is assessed by URR (urea reduction ratio).

URR= [pre dialysis urea-post dialysis urea /pre dialysis urea]*100

Reduction of URR more than 65% is adequate for CKD.

COMPLICATIONS

- Catheter related complications like infection, pneumothorax and bleeding. Tunneled catheters can be used up to 6 months.
- Thrombosis of AV fistula or graft. This can be treated with thrombolysis, angioplasty or stent placement.
- Intradialytic hypotension is mostly due to rapid ultrafiltration or depletion of intravascular volume. This can be managed with decreasing filtration rate and infusion of saline.
- Dialysis disequilibrium syndrome is due to rapid removal of toxins; patients may develop nausea, vomiting, headache and seizure.

RENAL TRANSPLANTATION

Renal replacement therapy in the form of renal transplantation is the treatment of choice for end stage renal disease. For these, kidneys from living donor and brain dead patients can be used. Living donor grafts have survival rate of 95 percent in 1 year, when compared to deceased donor which has 89% in one year. In order to reduce the discard rates of kidneys expanded criteria donor (ECD) and donors after cardiac death (DCD) are used. Usually ECD kidneys are used in older patients, those who are doing less well on other methods of renal replacement therapy.

DEFINITION OF AN EXPANDED CRITERIA DONOR (ECD)

- Deceased donor >60 years
- Deceased donor >50 years and hypertension and creatinine >1.5 mg/dL
- Deceased donor >50 years and hypertension and death caused by cerebrovascular accident (CVA)
- Deceased donor >50 years and death caused by CVA and creatinine >1.5 mg/dL

NON-HEART-BEATING DONOR [DONATION AFTER CARDIAC DEATH (DCD)]

- Brought in dead
- Unsuccessful resuscitation
- Awaiting cardiac arrest
- Cardiac arrest after brainstem death
- Cardiac arrest in a hospital patient

RECIPIENT SELECTION

Transplantation in patients who are on dialysis have a higher life expectancy than those who are remaining in dialysis alone. Mortality rate is higher in diabetic and older patients, but their survival rate is higher than the patients with dialysis alone. Every patient selected for dialysis should have risk benefit evaluation before transplantation. Absolute

contraindications for transplantation are HIV and active hepatitis, because of increased risk of opportunistic infection in these patients. Immunologic contraindications for transplantation are presence of preformed antibody in the donor. Antibodies causing early graft rejection are ABO blood group antigens and antibodies against human leukocyte antigen (HLA) class I (A, B, C) or class II (DR) antigens. These antibodies are routinely excluded by proper screening of the candidate's ABO compatibility, HLA typing of donor and recipient and direct cross-matching of candidate serum with lymphocytes of the donor.

DONOR SELECTION

Donors can be deceased or volunteer living donors. Living volunteer donors should be normal on physical examination and of the same major ABO blood group. It is possible to transplant a kidney of a type O donor into an A, B, or AB recipient. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries because the surgical procedure is difficult and the ischemic time of the transplanted kidney is long when there are vascular abnormalities. Deceased donors should be free of neoplastic disease, hepatitis, and HIV because of possible transmission to the recipient. Increased risk of graft failure exists when the donor is elderly or has renal failure and when the kidney has a prolonged period of ischemia and storage.

IMMUNOSUPPRESSION

Currently available immunosuppressive agents suppress all immune responses to fungus, malignant tumours and bacteria.

Commonly used immune suppressive agents are

1) **Glucocorticoids**

   Prednisone/prednisolone is generally used. It binds cytosolic receptors and heat shock proteins; Blocks transcription of IL-1,-2,-3,-6, TNF-α, and IFN-γ. Side effects are hypertension, glucose intolerance, dyslipidaemia, and osteoporosis.

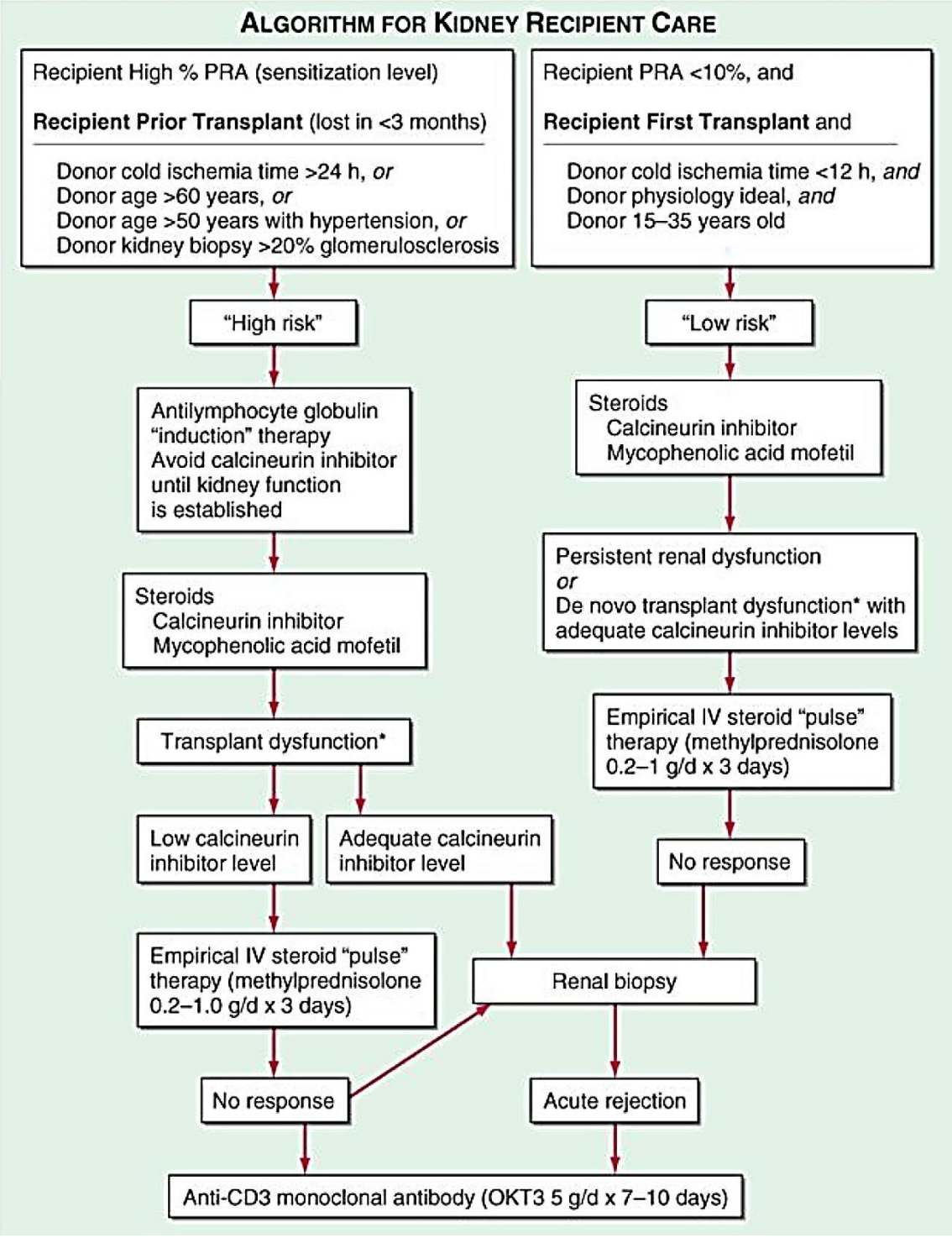
2) **Cyclosporine (CsA)**

   It forms trimolecular complex with cyclophilin and calcineurin. It blocks cytokine (e.g., IL-2) production however it stimulates TGF-β production. Side effects are Nephrotoxicity, hypertension, dyslipidaemia, glucose intolerance and hirsutism/hyperplasia of gums.

3) **Azathioprine**

   Hepatic metabolites of azathioprine inhibit purine synthesis. Side effect is marrow suppression (WBC > RBC > platelets).

4) **Mycophenolate mofetil (MMF):** It inhibits purine synthesis via inosine monophosphate dehydrogenase. Side effects are Diarrhoea/cramps and dose-related liver and marrow suppression.



CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate haemodialysis should be performed within 48 hours of surgery and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be prevented. Diuresis occurring in postoperative period, sometimes may be massive, due to inability of the tubules to concentrate urine.

Acute tubular necrosis (ATN) may cause immediate oliguria or may follow an initial short period of graft function. ATN is most likely when cadaveric donors have been under perfused or if the interval between cessation of blood flow and organ harvest (warm ischemic time) is more than a few minutes. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy.

Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is reduced drastically. Many centres avoid starting cyclosporine for the first several days, using ALG or a monoclonal antibody along with mycophenolic acid and prednisone until renal function is established.

OPPORTUNISTIC INFECTION

The most common opportunistic infections in renal transplant recipients are,

Peritransplant (<1 month)

Wound infections

Herpes virus

Oral candidiasis

Urinary tract infection

Early (1–6 months)

Pneumocystis carinii

Cytomegalovirus

Legionella

Listeria

Hepatitis B

Hepatitis C

Late (>6 months)

Aspergillus

Nocardia

BK virus (polyoma)

Herpes zoster

Hepatitis B

Hepatitis C

OTHER COMPLICATIONS OF TRANSPLANTATION

Myocardial infarction and stroke have higher incidence in chronic dialysis and transplant patients, particularly in diabetic patients. Other associated factors contributing to this increased incidence are use of glucocorticoids, sirolimus and hypertension. Cardiovascular system disease is contributing to more than 50% mortality in renal transplant recipients. So strict BP control and lipid profile monitoring is very important in this patients.

GLOMERULAR FILTRATION RATE

DEFINITION:

Glomerular filtration rate is defined as volume of fluid filtered by the glomerular capillaries per unit time. It is expressed as ml/min/1.73m^2 body surface area. Glomerular filtration rate is equal to clearance rate of the particular substance, when that particular substance is neither secreted nor absorbed from the tubular fluid.

NORMAL VALUES

In men approximate level of glomerular filtration rate is 125 to 135 ml/min/1.73m^2 and in women the level is 115 to 125 ml/min/1.73m^2. There is inter individual variability due to exercise, diurnal variation and protein intake. Gold standard substance that is used to measure GFR should have certain properties. They are free filterability across the glomerulus, no synthesis in the renal tubules, no reabsorption, not metabolized by the tubules and they should not alter the kidney function.

INULIN

Inulin is such a substance with most of the properties of ideal GFR measuring substance. It is a polymer of fructose, with molecular weight of 5000 D. In original description inulin was infused as continuous intravenous infusion. Multiple blood and urine samples are taken during the procedure. Bladder was catheterised to measure exact amount of urine; sometimes oral intake of water is advised to stimulate diuresis. Inulin is very difficult to handle and also this procedure is time consuming and invasive. So in order to avoid these disadvantages, GFR estimating formulas are introduced.

CLEARANCE METHODS

URINE CLEARANCE

Creatinine clearance is a measurement of clearance of endogenous biomarker. Atleast 12 to 24 hour urine collection is needed for adequate urine sample and also to achieve steady state of concentrations of substances. Blood sample for creatinine estimation is collected usually at the end of urine collection period. Serum or urine cystatin C could not be used to measure clearance study due to its metabolism and reabsorption in renal tubules.

PLASMA CLEARANCE

In this method glomerular filtration rate is measured by clearance of that substance from plasma over a period of time. Clearance is calculated by amount of the substance injected divided by AUC of plasma concentration over time. One of the drawbacks of this method is time needed to determine the final point of curve. Sometimes it may be very difficult to get repeated blood samples for substance concentration estimation.

EXOGENOUS FILTRATION MARKERS

Iothalmate

It is used as nonradioactive form and radioactive form. If nonradioactive form is used high performance liquid chromatography is used to measure the concentration. It is an iodine compound. If radioactive form is used it is given as subcutaneous injection. As it is an iodinated compound, to prevent thyroid uptake, cold iodine is also given along with iothalmate. Contraindication to its use is allergies to iodinated contrast.

IOHEXOL

Considering the hazards of the radioactive substances nonradioactive iohexol introduced. It can be given as bolus injection. Advantages of the iohexol over iothalmate are low cost, easy availability and stability in body. Adverse reactions are very low iohexol. One of the limitations is cost associated with high performance liquid chromatography. Some studies evaluated performance of this with other assay methods, which showed there is correlation between them.

Technetium-99 labelled di-ethehylene triamino penta-acetic acid is also used to measure GFR. It is filtered across glomerulus completely. There is less radiation exposure with 99mTc. Very minimal plasma binding leads to underestimation of GFR.

ACCURATE MEASUREMENT OF GFR ESSENTIAL IN

In most of the situations eGFR is enough to make decision about further planning. But in some clinical situations, glomerular estimation rate calculated based on serum creatinine is not that much accurate, so decision based on this inaccurate GFR leads to errors in patient management. So in some of situations, where estimation of glomerular filtration rate needed are,

CHRONIC ILLNESS

Because of reduced muscle mass in chronic illness, creatinine based equations measure inaccurate measurement of GFR. In these situations estimated GFR is inappropriately high when compared to measured-GFR. This may lead drug toxicity or kidney injury by contrast media.

DRUG DOSE ADJUSTMENT

If prolonged therapy and potential therapy is planned, we have to measure the glomerular filtration rate accurately. In most of the situations eGFR is enough, but if very toxic or very narrow therapeutic range drug should be used, it is better to measure GFR before starting treatment.

IMAGING TESTS

As toxicity of the iodinated contrast material is high in the presence of reduced GFR, we have to measure glomerular filtration rate accurately before using these agents. Current guidelines are to avoid gadolinium and to take preventive measures before using iodinated contrast agents.

MONITORING KIDNEY TRANSPLANT RECIPIENTS

Early detection of rejection of transplanted kidney is very much challenging in renal transplantation setup. So eGFR results are very difficult to interpret. Also serum creatinine is affected by other than GFR; they are usage of trimethoprim, effect of steroids on muscle, protein intake. In this situation measurement GFR is needed.

KIDNEY DONATION

Modification of diet in renal disease study formula underestimates GFR, when compared to standard methods. So if eGFR is inappropriately low, in otherwise healthy renal donor, it is mandatory to do glomerular filtration rate measurement.

INTERPRETATION OF SYMPTOMS OF KIDNEY FAILURE

Timing of access placement, pre-emptive transplantation and initiation of dialysis are generally determined based on an eGFR and patient symptoms. However, symptoms of uraemia are nonspecific. In patients with discrepancy between severity of reduction in eGFR and symptoms, it may be helpful to measure GFR.

MATERIALS AND METHODS:

STUDY POPULATION:

This study was conducted in 100 adult patients in a medical Intensive Care Unit of Government Rajaji hospital Madurai.

INCLUSION CRITERIA:

1) ICU stay > 48 hours and <1 week

2) Those with indwelling urinary catheter.

EXCLUSION CRITERIA:

1) Age less than 18 years

2) Pregnancy

3) Hemodialysis or peritoneal dialysis

4) Those on vasoactive drugs

5) Urine output < 400 ml/day

6) Patients receiving diuretics

7) Not willing to give consent.

DATA COLLECTION:

As per the inclusion and exclusion criteria study subjects were selected. After obtaining detailed informed consent from the patient or patient's attender if patient was illiterate, detailed history and physical examination was done. Blood and urine was collected from the subjects and the sample was sent to biochemistry lab for analysis.

LABORATORY INVESTIGATIONS:

1) Serum creatinine

2) Blood urea

3) 24 hours urine collection

4) Urine creatinine concentration in 24 hours sample

Serum creatinine and urine creatinine were measured by Jaffe's calorimetric method. Body weight was measured in kilogram. Height of the

patient was measured in meters. Urine was collected from 8 Am to next day 8 Am.; first sample was discarded. Urine volume measured in ml/day. 24 hours urine creatinine clearance was calculated by the following formula,

Creatinine clearance (ml/min) = (U * V)/ (P*1440), then this was converted into body surface area by the using following formula

CrCl= (U*V*1.73)/P*1440*BSA); here U is urine creatinine, V is urine volume in 24 hours, P is serum creatinine, BSA is body surface area.

Body surface area was calculated by Du Bois formula

Body surface area= $Weight^{0.425}$*$Height^{0.725}$*0.20247

Here weight in kilograms, height in meters.

ESTIMATED GLOMERULAR FILTRATION RATES

1) **Cockcroft- Gault formula**

EGFR = [(140-age) x (weight in Kg)] / [serum creatinine (mg/dl) x72]

Multiplied by 0.85 if patient is female; GFR calculated by CG formula was converted to 1.73 m^2 body surface area to compare with other two GFR.

2) **MDRD estimated creatinine clearance (ml/min/1.73m^2)**

EGFR = 186 x [serum creatinine (mg/dl)] $\wedge^{-1.154}$ x (age in years) $\wedge^{-0.203}$

If the subject or patient is female the GFR is multiplied by 0.742.

STUDY PROTOCOL

DESIGN OF STUDY:

Prospective cross sectional study

PERIOD OF STUDY: 4 months (JUNE 2014 TO SEPTEMBER 2014)

COLLABORATING DEPARTMENTS:

Department of Medicine

Department of Biochemistry

Department of Nephrology

ETHICAL CLEARANCE: obtained.

CONSENT: Individual written and informed consent.

ANALYSIS: statistical analysis

Data collected from the patients were analyzed with help of Statistical software packages Medcalc® (version 8.1) from Medcalc®

Belgium. Bland Altman curve was used to evaluate the relationship between the two GFR calculating methods. The mean percentage difference between estimated and measured clearance called as bias is also calculated. Correlation coefficient was calculated to assess the association between two methods.

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: NIL

STUDY POPULATION

100 adult patients from medical Intensive Care Unit of Government Rajaji Hospital, with atleast ICU stay of more than 48 hours.

RESULTS AND INTERPRETATIONS

Table-1 age distribution of study population

Age group	Male n (%)	Female n (%)	Total n (%)
10-20 years	3 (3)	1 (1)	4 (4)
20-30 years	11 (11)	9 (9)	20 (20)
30-40 years	12 (12)	10 (10)	22 (22)
40-50 years	13 (13)	6 (6)	19 (19)
50-60 years	12 (12)	9 (9)	21 (21)
60-70 years	10 (10)	3 (3)	13 (13)
70-80 years	1 (1)	0 (0)	1 (1)
Total	62	38	100

Comments:

Study population selected for this study varies from the age of 19 years to 71 years for male and from 19 years to 67 years for female. 65% of the study population belongs to the age group of <50 years. 35% of the study group belongs to the age group of >50 years.

Table-2: Descriptive statistics of age and sex distribution

Variable	N	Mean	SD	Minimum	Median	Maximum
MALE	62	44.194	15.128	19.000	45.000	71.000
FEMALE	38	41.421	13.912	19.000	37.500	67.000

This study consists of 62 male patients and 38 female patients.

Mean±SD of male patients are 44.194±15.128 and female patients are 41.421±13.912; with median age of 45 and 37.5 for male and female patients respectively.

Fig-7 Age distribution

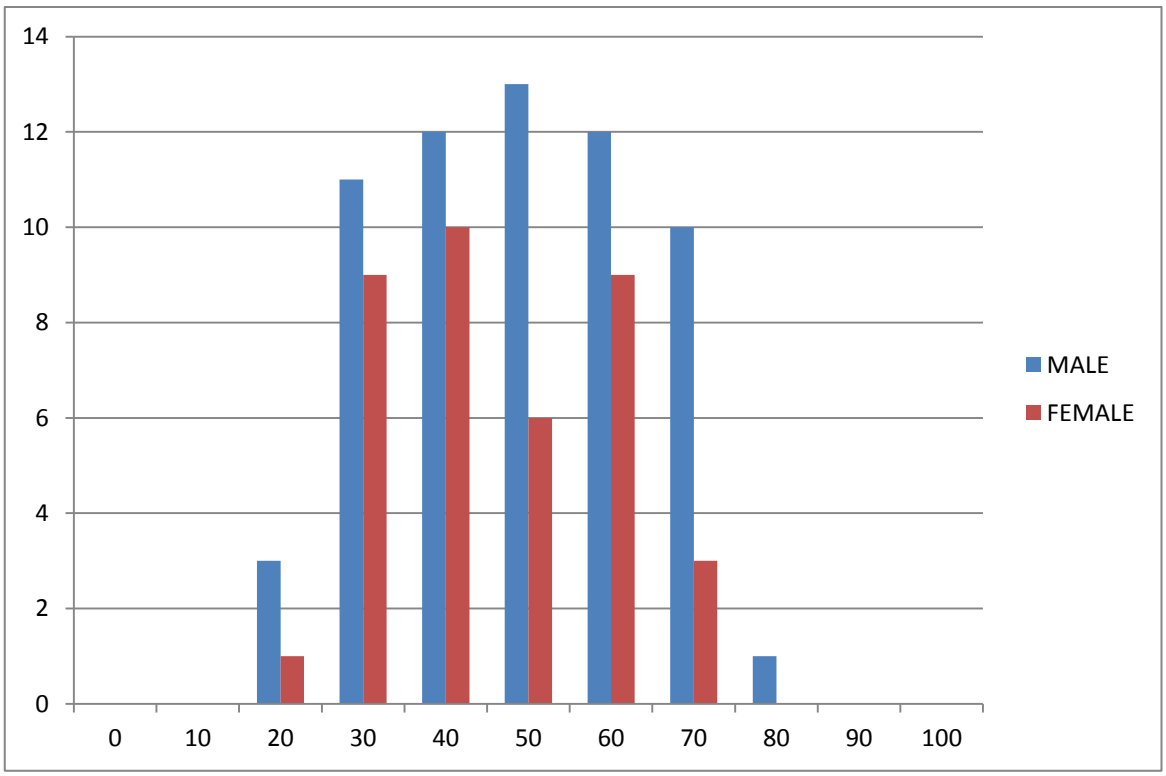
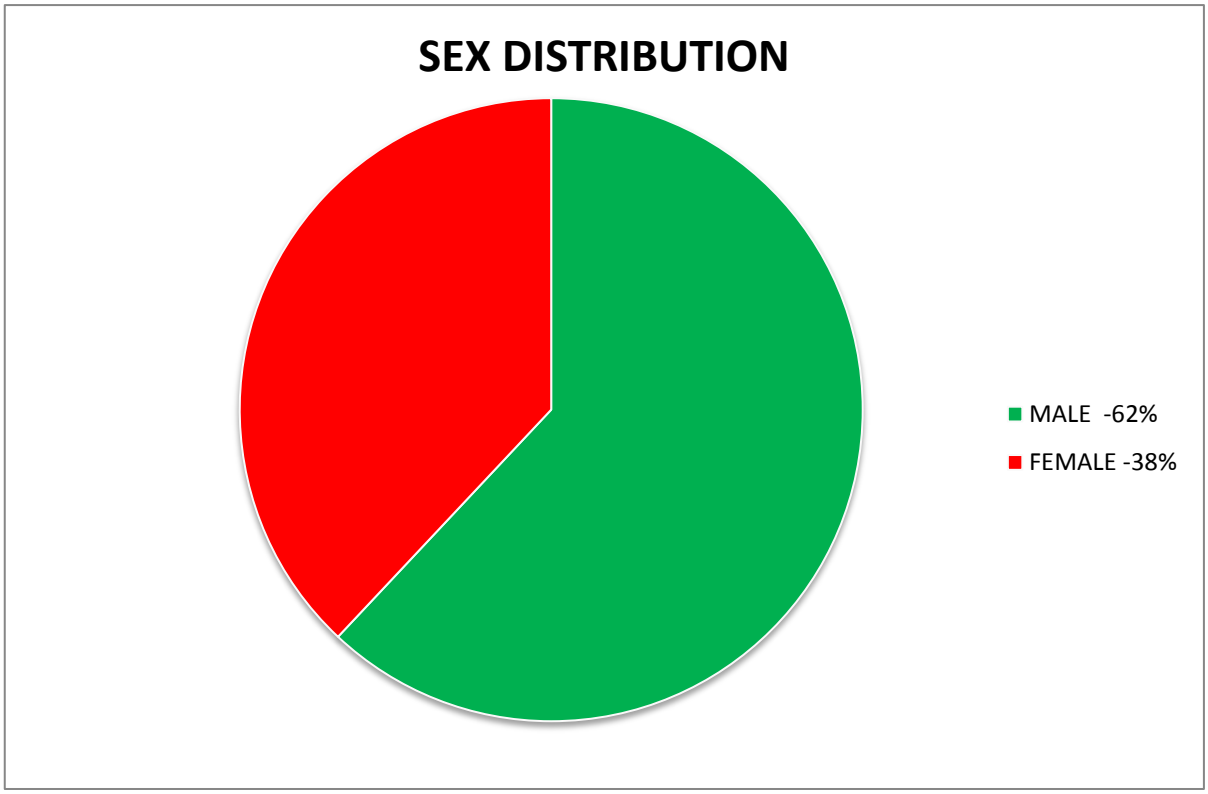


Table-3 Sex distribution

GENDER	FREQUENCY	PERCENT
MALE	62	62
FEMALE	38	38
TOTAL	100	100

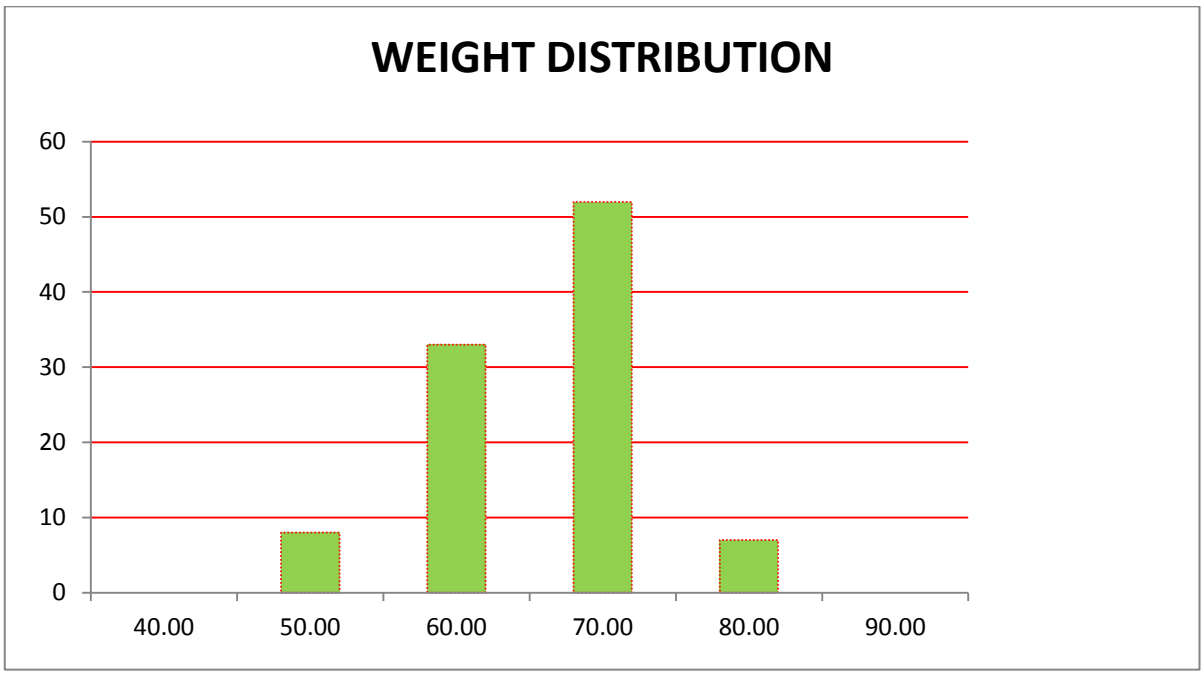
Fig-8 Sex distribution



Comments:

In this study 62% of the patients are male and remaining 38% are female

Fig-9 Descriptive statistics based on weight



Comments:

Minimum weight is 47kg and maximum weight is 78kg. Mean weight of the study population is 61.92kg with standard deviation of 7.021870596.

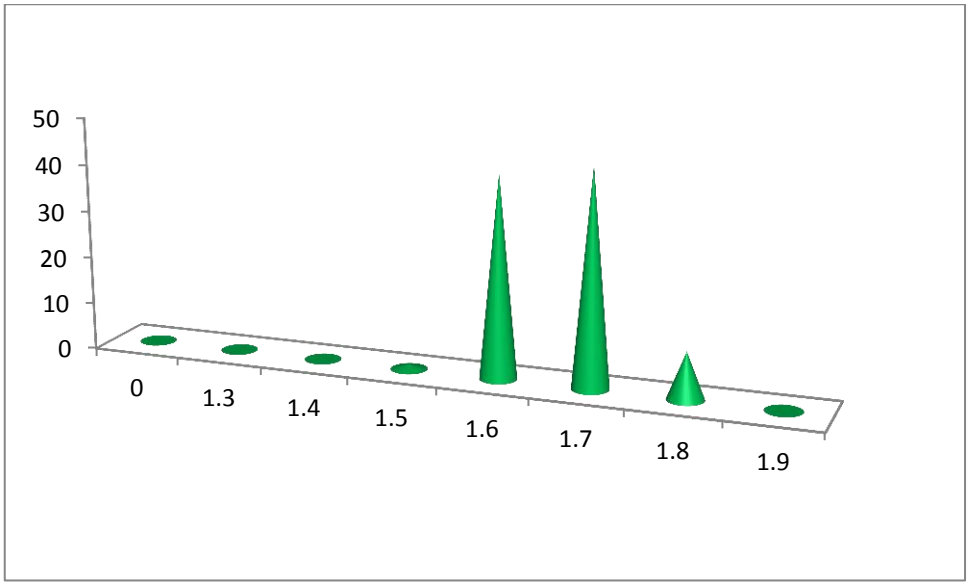


Fig-10 Height distribution of study population

Table-4 Epidemiological data of study population

PARAMETER	MEAN	SD	95% CI	MINIMUM	MAXIMUM
Age(years)	43.14	14.67	40.23-46.05	19	71
Weight(kg)	61.92	7.022	60.53-63.31	47	78
Height(m)	1.621	0.06347	1.608-1.633	1.490	1.78
S.creatinine (mg/dl)	1.664	0.4398	1.577-1.751	0.8	2.5
U.creatinine (mg/dl)	63.06	11.75	60.73-65.39	50	98
U.volume (ml)	1518	307.5	1457-1579	850	2100
BSA(m^2)	1.657	0.1014	1.636-1.677	1.44	1.89

Table-5 Mean and standard deviation comparison

METHOD	MEAN±SD	MINIMUM	MAXIMUM
24 Hr Urine CrCl	44.75±18.22	20.89	107.05
CG FORMULA	56.48±20.30	26.89	131.16
MDRD	48.71±19.69	23.16	115.54

Comments:

Mean±SD of the three methods are 44.75±18.22, 56.48±20.30, 48.71±19.69 respectively.

Table-6 Pearson correlation coefficient

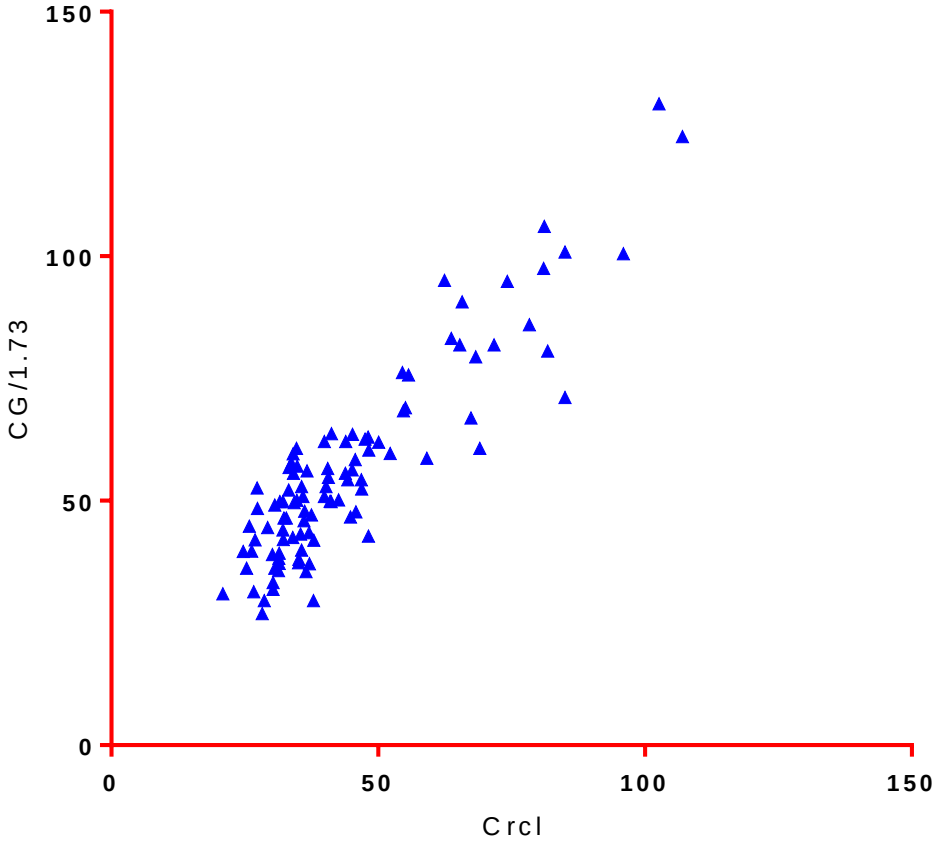
METHOD	BIAS	CORRELATION COEFFICIENT	P VALUE
CG/ 24 Hr Urine CrCl	11.73	0.9056	<0.0001
MDRD/ 24 Hr Urine CrCl	3.961	0.9303	<0.0001

Comments:

Both Cockcroft-gault and MDRD formula have positive bias 11.73 and 3.961 respectively, so both these formulas overestimate the glomerular filtration rate. Correlation coefficient for comparison of Cockcroft-Gault formula and 24 hour urine creatinine clearance is 0.90956 with p value of <0.0001. It indicates strong correlation between GFR calculated by Cockcroft-Gault formula and GFR measured by 24 hours urine creatinine clearance. Correlation coefficient for comparison between GFR calculated by MDRD formula with 24 hour urine creatinine clearance is 0.9303 with p value of <0.0001. It means there is strong correlation between GFR calculated by MDRD formula and GFR measured by 24 hours urine creatinine clearance.

Fig-11 Pearson correlation coefficient analysis

CG & 24 HOUR CREATININE CLEARANCE



Comments:

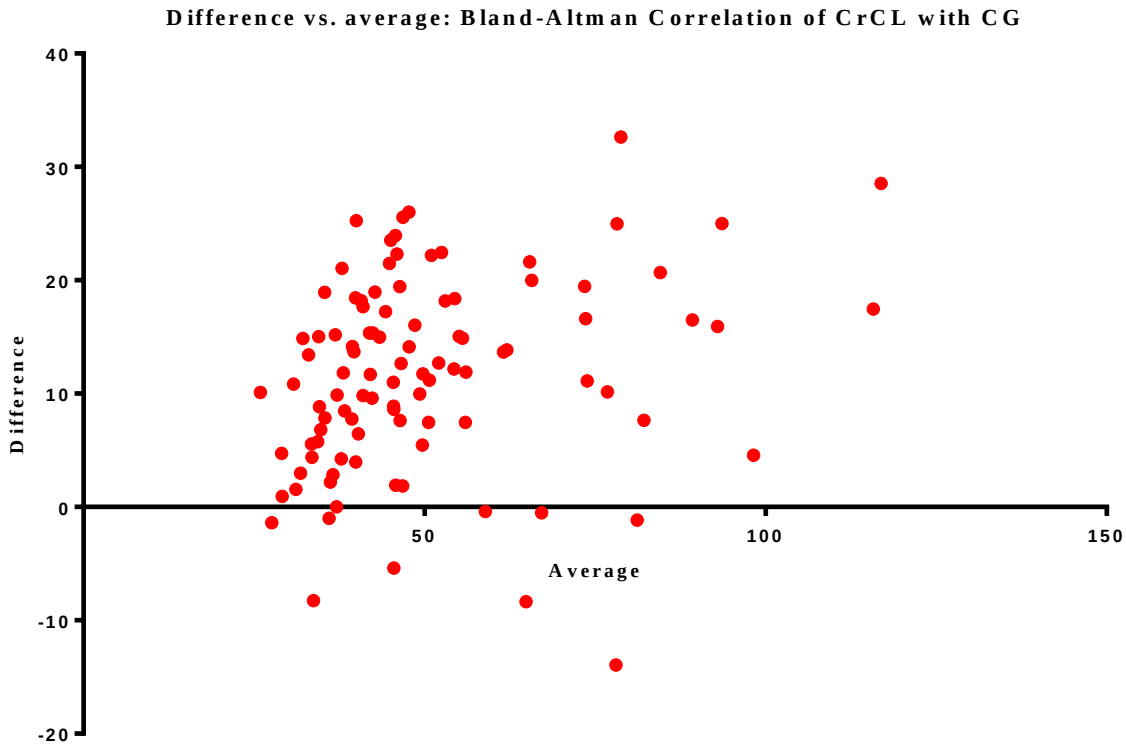
This shows correlation between GFR calculated by Cockcroft-Gault method and 24 hour urine creatinine clearance.

r (correlation coefficient) = 0.9056

95% confidence interval 0.8626 – 0.9356

P value <0.0001

Fig-12 Bland- Altman correlation analysis.

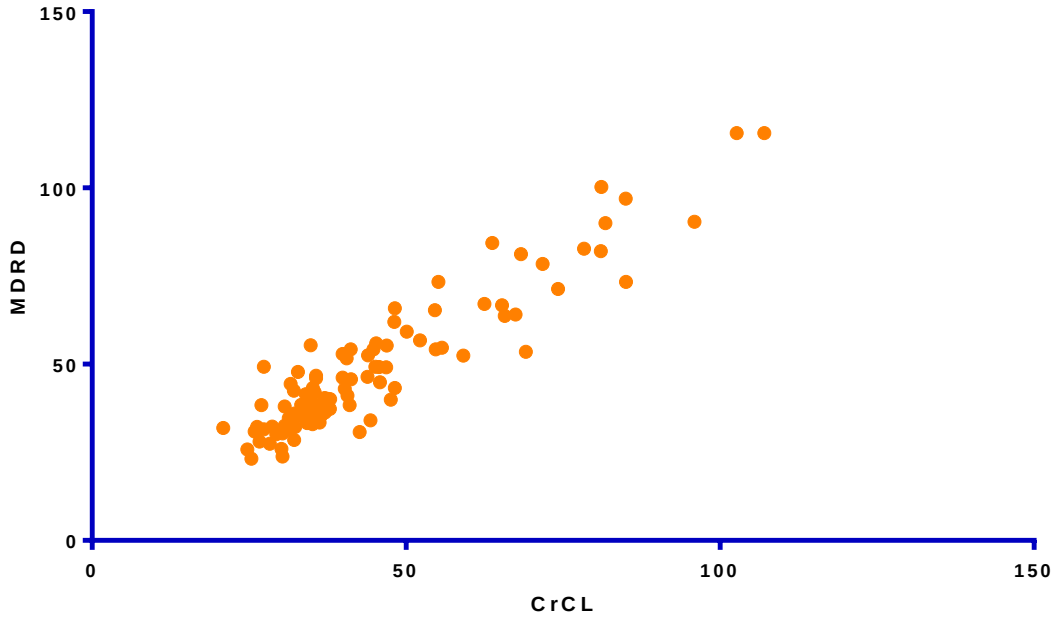


Comments:

Bias = 11.73

SD of bias 8.612

Fig-13 Pearson correlation coefficient analysis



Comments:

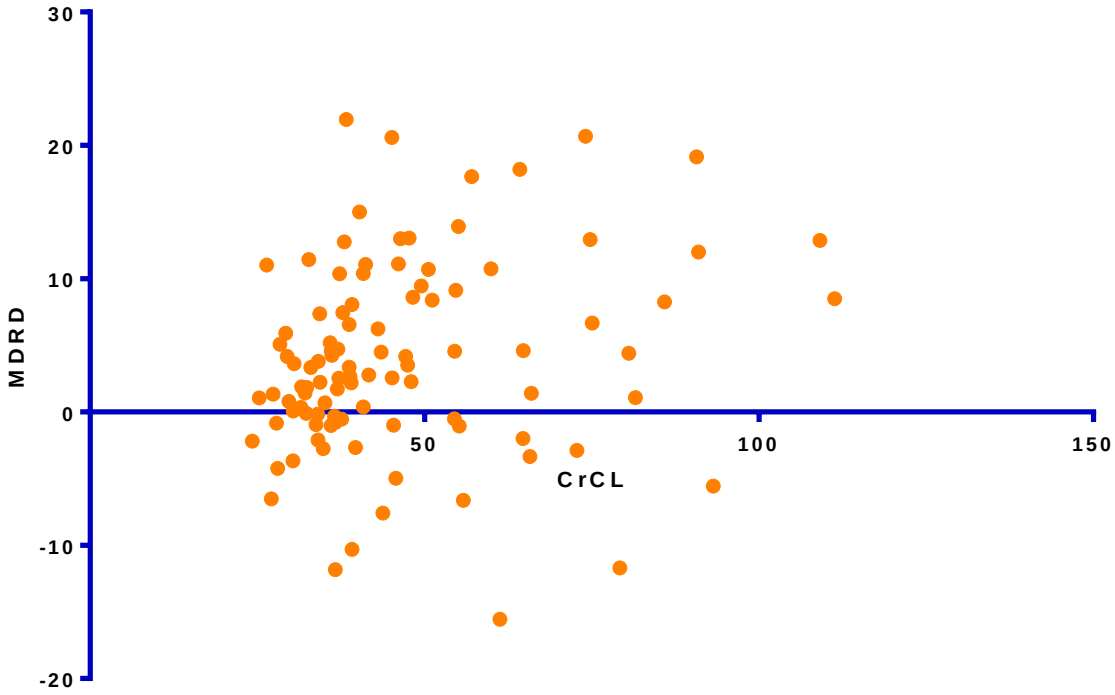
This shows correlation between GFR calculated by MDRD method and 24 hour urine creatinine clearance.

r (correlation coefficient) = 0.9303

95% confidence interval 0.8979 – 0.9526

P value <0.0001

Fig-14 Bland Altman correlation analysis



Comments:

Bias = 3.961

SD of bias 7.225

DISCUSSION

This study was conducted in intensive care unit of Government Rajaji hospital Madurai. Patients with age more than 18 years of age were included. Pregnant patients and patients on renal replacement therapy were excluded from the study. 100 patients were selected for GFR comparison study. Period of study was 4 months.

AGE AND SEX DISTRIBUTION OF THE STUDY

In this study mean age group of patients were 43.14 with standard deviation of 14.67; minimum age of the patient was 19 years and maximum age of the patient was 71 years. Out of 100 patients male patients were 62 and female patients were 38. (95% confidence interval for age was 40.23-46.05).[table 1]

In a study conducted by Mohit Kharbanda et al from Departments of Critical Care and Nephrology, AMRI Hospitals, Kolkata, India; mean age group was 65 years with 95% confidence of 58 to 68 years. Another study conducted by Magdi E. Al-Osali et al from Department of Internal Medicine, Al Nahdha Hospital, and Muscat, Oman included 158 patients; in this 115 patients belongs to age group of <70 years and 43 were >70 years.

In our study Mean±SD serum creatinine was 1.664±0.4398 (95% confidence interval 10557-1.751). In a study conducted by Mohit Kharbanda et al from Departments of Critical Care and Nephrology, AMRI Hospitals, Kolkata, India, mean serum creatinine was 1.06 mg/dl (95% CI 0.76 to 1.37. In another study conducted by Adnan Mustafa Zubairi et al from department of Clinical Pathology, Ziauddin University, Karachi in 2008 also showed Mean ±SD of 1.94 ± 1.55.

MEAN GFR AND CORRELATION COMPARISON

Estimation of glomerular filtration rate is important to decide about patient management, renal replacement therapy, and while administering drugs that is eliminated through kidney. In order to avoid toxicities of the drugs we have to monitor renal function by estimating glomerular filtration rate. This is very much important in ICU because, patient may get multiple drugs with different metabolic route for elimination. Glomerular filtration rate is the one of the best measure of kidney function. It can be measured by clearance of the exogenous substance. But these methods are costly and not easily available in hospitals. Endogenous substances such as creatinine also can be used to measure GFR, but it is affected by muscle mass, protein intake and exercise. In order to avoid these problems researchers found equations based on serum creatinine, body weight and age. Commonly used formulas are Cockcroft-Gault and MDRD formula. In this study we

compared the GFR measured by 24 hour urine creatinine clearance with CG and MDRD formula. There are some advantages with these formulas; they are simple, easy and repeatability.

The mean glomerular filtration rate measured by 24 hours urine creatinine clearance was 44.75ml/min/1.73m^2 (95% CI: 41.13 to 48.37). The mean glomerular rate calculated by Cockcroft-Gault formula was 56.48ml/min/1.73m^2 (95%CI: 52.45 to 60.51) and by MDRD formula was 48.71ml/min/m^2 (95% CI: 44.80 to 52.62).[Table 5] Correlation coefficient for comparison of Cockcroft-Gault formula and 24 hour urine creatinine clearance is 0.90956 with p value of <0.0001. Correlation coefficient for comparison between GFR calculated by MDRD formula with 24 hour urine creatinine clearance is 0.9303 with p value of <0.0001[Table 6].

However application of these formulas to calculate GFR, leads to overestimation of GFR as shown by positive Bias. In our study which is 11.73ml/min for Cockcroft-Gault equation and 3.961ml/min for MDRD equation[Table 6]. In a study conducted by Adnan Mustafa Zubairi et al from department of Clinical Pathology, Ziauddin University, Karachi showed bias of 16.5ml/min and 15.49ml/min for CG formula and MDRD formula respectively. In another study conducted by Mohit Kharbanda et al from Departments of Critical Care and Nephrology, AMRI Hospitals, Kolkata

also showed positive bias of 10.3ml/min and 5.2ml/min for CG and MDRD equations respectively.

LIMITATIONS OF THE STUDY

In this study we did not compare eGFR with gold standard methods such as inulin or iohexol clearance. In developing countries 24 hour urine creatinine clearance is used as a gold standard for GFR measurement. In the year 2005 Vila et al termed it as a gold standard. Serum creatinine is the net result of production, distribution, glomerular filtration, tubular secretion, and tubular re-absorption. Major source of creatinine is from metabolism of muscle. In critically ill patients creatinine production is decreased due to decreased intake of protein and reduced muscle mass. This decreased production may be one of the reasons for over estimation of glomerular filtration rate by serum creatinine based equations. So in critically ill patients, serum creatinine poorly reflects the change of glomerular filtration rate.

As inulin and other clearance studies are usually not available, we have to rely upon these eGFR formulas for glomerular estimation; this was conducted in the usual clinical setting. Even though these formulas overestimated the glomerular filtration rate, there is strong correlation between the formulas and 24 hours creatinine clearance.

CONCLUSION

As age, muscle mass, drugs, protein intake, exercise and sex affects the serum creatinine level it does not reflect the accurate renal function. And also as serum creatinine level lies within normal range till significant amount kidney function is lost, serum creatinine cannot be used to detect mild to moderate amount of renal dysfunction. Thus normal range of serum creatinine does not rule out kidney disease. GFR estimation is the main important step in assessing the renal function. In this study both CG and MDRD formulas have good correlation with 24 hour urine creatinine clearance. Because of convenience and cost, they can be used to assess the progression of disease. In clinical practice they have to interpret carefully because they tend to overestimate the actual glomerular filtration rate. Before applying into patients it is recommended that the study is to be conducted in large group of patients belonging to all ethnic groups.

SUMMARY

- In the intensive care setting estimation of glomerular filtration rate is important because, planning about treatment, renal replacement therapy, and deciding about drug dosage all depends upon the GFR.
- Originally substance that has been used should be filtered freely, neither reabsorbed nor secreted. Inulin is such substance, but it is not easily available.
- 24 hours urine creatinine clearance may be used, but we have to wait for 24 hours to get the report. Also some amount of tubular secretion leads to inappropriately high clearance.
- So formulas were developed to calculate eGFR that may be used in clinical situation to decide about treatment plan. These formulas are easy to apply and easily reproducible.
- Cockcroft-Gault and MDRD formulas are such formulas commonly used in clinical practice.
- Except one or two studies, no other studies evaluated it in Indian patients. So we compared these formulas with 24 hour urine creatinine clearance in estimating glomerular filtration rate.
- This study was conducted in 100 critically ill adult patients of Government Rajaji Hospital. For all patients 24 hour urine creatinine

clearance was measured and eGFR estimated by both CG and MDRD formulas.

- Bland Altman analysis and Pearson correlation coefficient was calculated.
- The mean GFR measured by 24 hours urine creatinine clearance was 44.75ml/min/1.73m2 (95% CI: 41.13 to 48.37). The mean glomerular rate calculated by Cockcroft-Gault formula was 56.48ml/min/1.73m2 (95%CI: 52.45 to 60.51) and by MDRD formula was 48.71ml/min/m2 (95% CI: 44.80 to 52.62).
- Correlation coefficient for comparison of CG formula/24 hour urine creatinine clearance and MDRD/24 hour urine clearance were 0.90956 with p value of <0.0001 and 0.9303 with p value of <0.0001 respectively.
- Both formulas had strong correlation with urine clearance. But MDRD had better correlation than CG formula.
- Bias is defined as the mean difference between calculated and measured GFR.
- In our study bias was 11.73ml/min for Cockcroft-Gault equation and 3.961ml/min for MDRD equation.
- It indicates over estimation of GFR by both these formulas when compared to 24 hour urine creatinine clearance.

BIBLIOGRAPHY

1) Assessment of accuracy of Cockcroft-Gault and MDRD formulae in critically ill Indian patients. Kharbanda M, Majumdar A, Basu S, Todi S. Indian J Crit Care Med 2013;17:71-5.

2) Assessment of Glomerular Filtration Rates by Cockcroft-Gault and Modification of Diet in Renal Disease Equations in a Cohort of Omani Patients. Magdi E. Al-Osali, Salim S. Al-Qassabi, Saud M. Al-Harthi. Sultan Qaboos University Med J, February 2014, Vol. 14, Iss. 1, pp. e72-79, Epub. 27TH Jan 14.

3) The Glomerular Filtration Rate: Comparison of various predictive equations basedon Serum Creatinine with Conventional Creatinine Clearance test in PakistaniPopulation Adnan Mustafa Zubairi, Arif HussainDepartment of Chemical Pathology, Ziauddin University, Karachi (JPMA 58:182;2008).

4) Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.

5) Wilson RF, Soulilier G. The validity of two hour creatinine clearance studies in critically ill patients. Crit Care Med 1980;8:281-4.

6) Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.

7) Cherry RA, Eachempati SR, Hydo L, Barie PS. Accuracy of short duration creatinine clearance determinations in predicting 24-hour creatinine clearance in critically ill and injured patients. J Trauma 2002;53:267-71

8) Pesola GR, Akhavan I, Madu A, Shah NK, Carlon GC. Prediction equation estimates of creatinine clearance in the intensive care unit. Intensive Care Med 1993;19:39-43.

9) Gaspari F, Perico N, Remuzzi G. Application of newer clearance techniques for the determination of glomerular filtration rate. Curr Opin Nephrol Hypertens 1998; 7:675–80.

10) Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int 1985; 28:830–8.

11) Zubairi AM, Hussain A. The glomerular filtration rate: Comparison of various predictive equations based on serum creatinine with conventional

creatinine clearance test in Pakistani population. J Pak Med Assoc 2008; 58:182–5.

12) Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol 2005; 16:763–73.

13) Alcantara P, Goncalves F, Moreira C, Gonzalez MA. [Assessment of glomerular filtration rate in a hospital population. Comparison of two methods]. Acta Med Port 1998; 11:767–72.

14) Srinivas S, Annigeri RA, Mani MK, Rao BS, Kowdle PC, Seshadri R. Estimation of glomerular filtration rate in South Asian healthy adult kidney donors. Nephrology (Carlton) 2008; 13:440–6.

15) Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, et al. Estimation of glomerular filtration rate in diabetic subjects: Cockcroft formula or modification of diet in renal disease study equation? Diabetes Care 2005; 28:838–43.

16) Stevens LA, Levey AS. Measurement of kidney function. Med Clin North Am 2005; 89: 457-73.

17) Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guideline for chronic kidney

disease: evaluation, classification and stratification. Ann Intern Med 2003; 139: 137-47.

18) Evans W, Lensmeyer JP, Kirby RS, Malnory ME, Broekhuizen FF. Two-hour urine collection for evaluating renal function correlates with 24-hour urine collection in pregnant patients. J Matern Fetal Med 2000;9:233-7.

19) Du Bois D, Du Bois EF. A formula to estimate the approx surface area if height and weight be known. Arch Intern Med 1916;17:863-71.

20) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.

21) Hailemeskel B, Namanny MD, Kurz A. Estimating aminoglycoside dosage requirements in patients with low serum creatinine concentrations. Am J Health Syst Pharm 1997;54:986-7.

22) Jung K, Jung M. Cystatin C: A promising marker of glomerular filtration rate to replace creatinine. Nephron 1995;70:370-1

23) Du Bois D, Du Bois EF. A formula to estimate the approx surface area if height and weight be known. Arch Intern Med 1916;17:863-71.

24) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10

25) Beck GJ, Berg RL, Coggins CH, Gassman JJ, Hunsicker LG, Schluchter MD, et al. Design and statistical issues of the Modification of Diet in Renal Disease Trial. The Modification of Diet in Renal Disease Study Group. Control Clin Trials 1991;12:566-86

26) Cherry RA, Eachempati SR, Hydo L, Barie PS. Accuracy of short duration creatinine clearance determinations in predicting 24-hour creatinine clearance in critically ill and injured patients. J Trauma 2002;53:267-71

27) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.

28) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002; 39:S1–266.

29) Srinivas S, Annigeri RA, Mani MK, Rao BS, Kowdle PC, Seshadri R. Estimation of glomerular filtration rate in South

Asian healthy adult kidney donors. Nephrology (Carlton) 2008; 13:440–6.

30) Gaspari F, Perico N, Remuzzi G. Application of newer clearance techniques for the determination of glomerular filtration rate. Curr Opin Nephrol Hypertens 1998; 7:675–80

31) Marshall WJ. Biochemical tests of renal function. In: Marshall WJ, Bangert SK, eds. Clinical Chemistry 5th ed. London: Mosby, 2004, 65-68.

32) Mahajan S, Mukhiya GK, Singh R, Tiwari SC, Kalra V, Bhowmik DM, et al. Assessing glomerular filteration rate in healthy Indian adults: a comparison of various prediction equations. J Nephrol 2005; 18: 257-61.

33) Wulkan R, den Hollander J, Berghout A. Cystatin C: Unsuited to use as a marker of kidney function in the intensive care unit. Crit Care 2005;9:531-2.

34) Hailemeskel B, Namanny MD, Kurz A. Estimating aminoglycoside dosage requirements in patients with low serum creatinine concentrations. Am J Health Syst Pharm 1997;54:986-7.

35) Herget-Rosenthal S, Trabold S, Pietruck F, Holtmann M, Philipp T, Kribben A. Cystatin C: Efficacy as screening test for reduced glomerular filtration rate. Am J Nephrol 2000;20:97-102.

36) Finney H, Newman DJ, Price CP. Adult reference ranges for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem 2000;37:49-59.

PROFORMA

Name:

Age/Sex:

Occupation:

Past history:

Drug history:

Family history:

Clinical examination:

General examination:

1)Height

2)weight

3)BMI

Vitals:

PR-

BP-

RR -

SpO2-

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

1) Serum creatinine

2) Blood urea

3) 24 hours urine collection

4) 1 hour urine collection

5) Urine creatinine concentration in 1 hour sample

6) Urine creatinine concentration in 24 hours sample

ABBREVIATIONS

GFR- Glomerular Filtration Rate

DTPA- Diethyl Triamine Penta-Acetic Acid

EDTA- Ethylene Diamine Tetraacetic Acids

MDRD- Modification of Diet in Renal Disease

CG- Cockcroft Gault

AKI- Acute Kidney Injury

CKD- Chronic Kidney Disease

VEGF- Vascular endothelial growth factor

JG- Juxta glomerular apparatus

RAAS- Renin angiotensin aldosterone system

ADH- Antidiuretic hormone

ACE- Angiotensin converting enzyme

ARB- Angiotensin receptor blocker

ANA- Antinuclear antibody

ANCA- Antinuclear cytoplasmic antibody

ADPKD- Autosomal polycystic kidney disease

KDOQI- Kidney disease outcome quality initiative

NKF- National kidney foundation

CAPD- Continuous ambulatory peritoneal dialysis

CCPD- Continuous cycling peritoneal dialysis

CRRT- Continuous renal replacement therapy

ECD- Expanded criteria donor

DCD- Donors after cardiac death

ATN- Acute tubular necrosis

MASTER CHART

S.NO	AGE	SEX	WT	HT	Scr	U.CR	U Volume	BSA	CrCL	MDRD	CG/1.73
1	32	M	63	1.68	1.8	52	1763	1.72	35.66	46.71	52.9
2	52	M	52	1.62	2.3	56	1100	1.54	20.89	31.90	31.0
3	45	M	67	1.58	0.9	55	1950	1.68	84.99	96.99	100.9
4	63	M	58	1.67	2.2	55	1575	1.65	28.68	32.29	29.6
5	48	M	67	1.72	1.9	50	2100	1.79	37.06	40.41	43.5
6	25	M	59	1.63	1.7	78	1750	1.63	59.10	52.46	58.7
7	54	M	59	1.54	1.8	52	1600	1.57	35.45	42.00	43.2
8	67	M	58	1.59	1.6	54	1400	1.59	35.67	46.05	39.9
9	21	M	48	1.72	1.9	63	1280	1.55	32.80	47.80	46.5
10	34	M	65	1.67	1.7	65	1700	1.73	45.11	49.28	56.3
11	19	M	54	1.62	1.5	85	1550	1.57	67.42	64.08	66.9
12	47	M	68	1.7	2	54	1875	1.79	34.02	38.26	42.5
13	35	M	57	1.66	2.1	58	1325	1.63	26.97	38.39	42.0
14	39	M	74	1.65	1.3	51	2100	1.81	54.58	65.32	76.2
15	65	M	69	1.59	0.9	53	1980	1.71	81.75	90.01	80.6
16	49	M	64	1.62	1	51	1750	1.68	63.74	84.41	83.2
17	57	M	68	1.63	1.1	75	1800	1.73	85.04	73.33	71.1
18	33	M	64	1.57	1.8	55	1965	1.64	43.87	46.42	55.6
19	68	M	69	1.55	2	73	1400	1.68	36.50	35.49	35.5
20	48	M	71	1.64	2.1	74	1350	1.77	32.22	36.01	42.1
21	59	M	65	1.69	1.2	58	1450	1.75	48.22	65.87	60.4
22	57	M	65	1.64	1.1	75	1150	1.71	55.14	73.33	69.0
23	65	M	67	1.67	1.9	68	1250	1.75	30.65	38.00	36.2
24	19	M	70	1.59	0.9	68	1950	1.72	102.6	115.54	131.2
25	64	M	62	1.72	1.4	58	1560	1.73	44.79	54.23	46.7
26	28	M	61	1.78	1.5	60	1840	1.76	50.10	59.23	62.0
27	35	M	65	1.54	1	79	1650	1.63	95.94	90.38	100.5
28	41	M	58	1.68	2.5	55	1900	1.66	30.32	30.40	33.3
29	28	M	63	1.66	2	52	1750	1.70	32.14	42.50	49.8
30	65	M	71	1.62	1.7	72	1665	1.76	48.19	43.21	42.8
31	32	M	68	1.74	1.6	88	1900	1.82	69.06	53.51	60.7
32	58	M	64	1.67	1.4	57	1650	1.72	46.93	55.32	52.4
33	25	M	55	1.59	1.8	78	1400	1.56	46.84	49.11	54.3
34	39	M	57	1.64	1.5	54	1300	1.62	34.80	55.38	57.1
35	47	M	69	1.68	1.7	53	1900	1.78	39.91	46.15	50.9
36	38	M	67	1.75	1.6	56	1750	1.81	40.56	51.67	56.6
37	21	M	54	1.7	1.2	67	1650	1.62	68.29	81.23	79.4
38	29	M	62	1.59	2.2	58	1865	1.64	36.08	37.80	45.9
39	54	M	69	1.52	1	64	1690	1.66	78.35	82.76	86.0
40	46	M	57	1.69	2.1	63	1700	1.65	37.10	36.32	37.1

S.NO	AGE	SEX	WT	HT	Scr	U.CR	U Volume	BSA	CrCL	MDRD	CG/1.73
41	35	M	68	1.62	1.6	51	1980	1.73	43.93	52.54	62.1
42	19	M	67	1.65	0.9	68	2050	1.74	107.0	115.54	124.5
43	27	M	69	1.58	2.2	61	2100	1.71	41.01	38.35	49.9
44	55	M	78	1.57	1.4	68	1386	1.79	45.22	55.92	63.6
45	48	M	67	1.68	1.6	53	1210	1.76	27.34	49.28	52.6
46	58	M	65	1.64	2.1	85	1100	1.71	31.31	34.65	35.7
47	54	M	68	1.63	1.7	90	1250	1.73	45.85	44.86	47.7
48	39	M	64	1.55	2.4	59	1450	1.63	26.29	32.19	39.7
49	51	M	74	1.75	1.4	64	1800	1.89	52.24	56.79	59.7
50	24	M	69	1.73	1.7	55	1870	1.82	39.90	52.89	62.1
51	44	M	65	1.69	2.3	75	1565	1.75	35.11	33.00	37.3
52	28	M	58	1.57	2.1	94	1100	1.58	37.51	40.17	47.1
53	64	M	67	1.67	1.4	51	1650	1.75	41.18	54.23	49.8
54	71	M	54	1.66	1.9	51	1870	1.59	37.86	37.33	29.6
55	45	M	58	1.53	2.3	69	1350	1.55	31.44	32.85	37.2
56	57	M	75	1.58	1.7	51	1550	1.77	31.61	44.37	49.8
57	33	M	58	1.73	1.4	55	1725	1.69	48.12	62.03	63.0
58	21	M	68	1.76	1	90	1375	1.83	81.11	100.25	106.1
59	65	M	59	1.65	1.7	65	1260	1.65	35.15	43.21	38.0
60	42	M	67	1.63	2.4	54	2000	1.72	31.38	31.71	38.2
61	68	M	69	1.67	2.5	55	1900	1.78	28.28	27.43	26.9
62	41	M	64	1.63	1.1	75	1480	1.69	71.74	78.41	81.9
63	35	F	58	1.51	1.7	51	1560	1.53	36.67	36.35	56.1
64	23	F	49	1.53	1.5	53	1400	1.44	41.25	45.74	63.7
65	24	F	57	1.49	2.1	68	1650	1.51	42.59	30.75	50.2
66	36	F	49	1.61	1	65	1250	1.50	65.29	66.68	81.9
67	28	F	53	1.64	1.9	69	1300	1.57	36.21	33.46	47.9
68	19	F	50	1.58	2.1	51	1650	1.49	32.36	32.25	46.5
69	65	F	64	1.57	2.2	63	1450	1.64	30.34	23.81	31.9
70	54	F	47	1.59	1.7	72	900	1.46	31.46	33.29	39.3
71	45	F	68	1.6	1	60	1560	1.71	65.73	63.73	90.7
72	46	F	52	1.57	0.8	58	1400	1.51	81.00	82.08	97.5
73	58	F	65	1.63	1.1	62	1375	1.70	54.74	54.22	68.4
74	57	F	57	1.65	1.2	57	1300	1.62	45.71	49.22	58.4
75	35	F	58	1.58	2.1	81	1100	1.58	32.17	28.49	44.0
76	21	F	55	1.63	1.9	98	850	1.58	33.24	35.47	52.2
77	26	F	51	1.57	2.4	75	1200	1.49	30.17	25.94	39.0
78	58	F	63	1.55	1.4	59	1300	1.62	40.67	41.05	54.8
79	56	F	68	1.6	1.6	72	1100	1.71	34.76	35.44	50.1
80	54	F	72	1.59	1.5	58	1250	1.74	33.28	38.46	56.8
81	36	F	57	1.58	2.5	83	1000	1.57	25.36	23.16	36.2
82	24	F	56	1.62	2	55	1475	1.59	30.66	32.53	49.1
83	67	F	49	1.53	1.9	64	950	1.44	26.68	28.02	31.4

S.NO	AGE	SEX	WT	HT	Scr	U.CR	U Volume	BSA	CrCL	MDRD	CG/1.73
84	54	F	57	1.54	1.5	71	975	1.54	35.92	38.46	50.9
85	35	F	62	1.54	1.8	85	1250	1.60	44.33	34.03	54.3
86	31	F	63	1.59	1.6	58	1800	1.65	47.55	39.96	62.6
87	46	F	49	1.61	1.4	51	1375	1.50	40.25	43.03	52.9
88	48	F	69	1.54	1.5	58	1250	1.67	34.68	39.39	60.7
89	56	F	67	1.57	1.8	50	1300	1.68	25.87	30.94	44.8
90	34	F	53	1.52	2.3	53	1325	1.48	24.74	25.80	39.6
91	28	F	54	1.53	2	57	1200	1.50	27.36	31.53	48.4
92	65	F	47	1.57	1.4	50	1275	1.44	37.93	40.11	41.9
93	47	F	65	1.65	1.9	51	1560	1.72	29.32	30.12	44.5
94	39	F	58	1.57	1.8	83	975	1.58	34.25	33.29	49.6
95	35	F	61	1.58	1	51	1650	1.62	62.46	67.06	95.1
96	26	F	67	1.65	1.9	67	1400	1.74	34.12	33.96	55.6
97	27	F	58	1.61	1.7	59	1300	1.61	33.75	38.32	57.7
98	47	F	67	1.67	0.9	50	1950	1.75	74.22	71.33	94.9
99	34	F	55	1.57	1.2	52	1650	1.54	55.71	54.66	75.7
100	55	F	68	1.54	1.4	55	1200	1.66	34.04	41.49	59.6

Ref.No.6506/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 31. 07 .2014

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 – Ethics Committee Meeting – Meeting Minutes - for July 2014 – Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 22nd July 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following project was approved by the committee

Name of the PG Student	Course	Name of the Project	Remarks
Dr.M.Rathinam Drrathinam86@gmail.com	PG in MD (General Medicine) Madurai Medical College & Rajaji Hospital, Madurai	A comparative study on accuracy of Cockcroft-Gault and MDRD formulae with 24 hour urine creatinine clearance in estimating glomerular filtration rate.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance.
   She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary
Ethical Committee

Chairman
Ethical committee

31.7.14
DEAN/Convenor
Madurai Medical College & Govt.
Rajaji Hospital, Madurai.

To
The above Applicant
-thro. Head of the Department concerned

A COMPARATIVE STUDY ON ACCURACY OF COCKCROFT-GAULT AND MDRD FORMULAE WITH 24 HOUR URINE CREATININE CLEARANCE IN ESTIMATING GLOMERULAR FILTRATION RATE

Dissertation submitted for

DOCTOR OF MEDICINE

Branch I – GENERAL MEDICINE

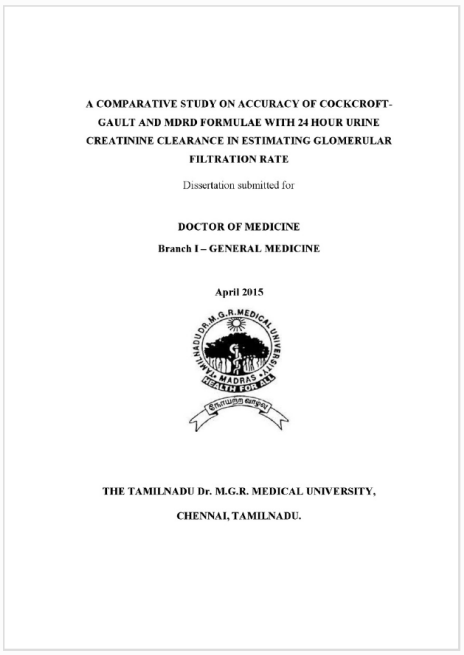
April 2015

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201211115.md General Medicine RA…
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	A COMPARATIVE STUDY ON ACCU…
File name:	Thesis_full_for_turnitin.pdf
File size:	92.17K
Page count:	110
Word count:	15,165
Character count:	85,129
Submission date:	24-Sep-2014 03:53AM
Submission ID:	454218248



A COMPARATIVE STUDY ON ACCURACY OF COCKCROFT-GAULT AND MDRD FORMULAE WITH 24 HOUR URINE CREATININE CLEARANCE IN ESTIMATING GLOMERULAR FILTRATION RATE

Dissertation submitted for

DOCTOR OF MEDICINE

Branch I – GENERAL MEDICINE

April 2015

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI, TAMILNADU.