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Review article
Understanding Kidney Disorders in times of Coronavirus-COVID19-A

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ABSTRACT

Kidney is one of the vital organs of the body that performs several important functions in the body viz, excretion of waste products resulting from protein metabolism, regulation of acid base balance by excretion of H+ ions (acidification) and bicarbonate ions, regulation of salt water balance by hormones secreted both intra and extra-renally, formation of renin and erythropoietin and there by a role in the regulation of blood pressure and erythropoiesis respectively. Presently whole world is witnessing the rise of the deadly pandemic caused due to novel coronavirus or COVID19. In such testing times the persons suffering from comorbidities such as hypertension, cardiac disorders, diabetics or kidney disorders are at greater risk to this life threatening virus. Therefore, people suffering from such disorders especially with kidney disease, transplant recipients, and people with other severe chronic medical conditions are at higher risk for developing serious complications from COVID-19. The present review highlights about the present scenario of kidney disorders in times of Covid-19 through the available data on electronic platform. Moreover the causes, diagnosis, stages, types, treatment, signs & symptoms, nephrotoxicity and nephrotoxins in respect of various kidney disorders have been briefly explained.

1. Introduction

Kidney is one of the vital organs of the body that performs several important functions in the body viz, excretion of waste products resulting from protein metabolism, regulation of acid base balance by excretion of H+ ions (acidification) and bicarbonate ions, regulation of salt water balance by hormones secreted both intra and extra-renally, formation of renin and erythropoietin and there by a role in the regulation of blood pressure and erythropoiesis respectively. Most often it is attacked by a variety of micro-organism, drugs, and chemicals that alter the renal functions with adverse effects on the human health. As per Global Burden of disease GBD study in 2015, about 1.2 million people died from kidney failure, an increase of 32% since 2005. In 2010, an estimated 2.3–7.1 million people with end-stage kidney disease died without access to chronic dialysis. Additionally, each year, around 1.7 million people are believed to die from acute kidney injury. Overall, an estimated 5–10 million people die annually from kidney disease [1]. Presently, whole world is witnessing the rise of the deadly pandemic caused due to novel coronavirus or COVID19. In such testing times the persons suffering from comorbidities such as hypertension, cardiac disorders, diabetics or kidney disorders are at greater risk to this life threatening virus. Therefore, people suffering from such disorders especially with kidney disease, transplant recipients, and people with other severe chronic medical conditions are at higher risk for developing serious complications from COVID-19. It is a known fact that people which are on dialysis have weaker immune systems, making it harder to fight infections. However, it is highly recommended that patients need to continue with their regularly scheduled dialysis treatments. Patients with kidney disorders either Acute Renal Failure or Chronic Renal disorders usually are advised to take immunosuppressive medicines. These medicines work by keeping the defense system or immune system of the patients body less active, which results in making the body harder to fight infections or any disorder. It is literally important to keep taking these medicines. It is also important to wash hands, maintain good hygiene and follow the recommendations from their healthcare team. [2].

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Kidney Disorders and Coronavirus

The data was collated from the website of National Kidney Foundation (NKF) i.e www.kidney.org based in New York City of U.S. The National Kidney Foundation (NKF) is the largest, most comprehensive, and longstanding patient-centric organization dedicated to the awareness, prevention, and treatment of kidney disease in the U.S. While accessing this website on 06.06.2020 regarding research on COVID-19 and kidney disease it has explained the following based on available recent data:-

The data which was collected from Wuhan city of China and New York City of United States, showed that an estimated 14–30% of COVID-19 patients lose kidney function and amongst them the patients in ICU required dialysis. Similarly, in hot spots or active virus areas within the United States such as New York City, early estimates indicated that 20-40% of COVID-19 ICU patients developed kidney failure and needed urgent renal care and dialysis. While new data from the same city showed that the mortality rate for kidney transplant patients from COVID-19 is as high as a staggering 30%. While going in the details of the same data it was found that in addition to this scenario some health disparities, some racial and ethnic minority groups are also at increased risk for both kidney disease and COVID-19 and are, therefore, relatively more vulnerable. These disparities are related to systemic, clinical, social, patient, and clinician factors. Overall, minority groups are at increased risk of progressing from developing CKD and experiencing more rapid progression of CKD to end-stage kidney disease (ESKD). Non-Hispanic African-American and Hispanic people experience more rapid decline of kidney function than non-Hispanic whites. Similarly, African Americans and Hispanics are also less likely to be treated with kidney transplant than Whites. There is no hiding from the fact that racial and ethnic minority groups have been hit disproportionately hard by the COVID-19 pandemic. Taking example such as, higher COVID-19 mortality in African-American populations has been reported in the areas of New Orleans, Chicago, Milwaukee, and Detroit. Almost 70% of the people who have died from coronavirus in areas like Louisiana are African-American, who amount up 32% of the population. African Americans are 14% of the population in Michigan, but represent 40% of COVID-19 deaths. The fact is that the according to the data released by the New York City Department of Health on May 6, 2020, African Americans and Hispanics represent two-thirds of COVID-19 hospitalizations and deaths in the city, while comprising just over half of the city's population. The reasons for these disparities include: lack of healthcare access; high percentages of minorities working in “essential” and low-wage jobs with high public exposure; population density in low-income areas making social distancing difficult; high percentages of comorbid conditions in minority populations; lack of health insurance; among other factors. Unemployment, food insecurity, and unstable or substandard housing conditions have also been implicated as contributing factors. [3].

What is a way ahead- A solution at disposal

· Extra public health precautions like social distancing and face mask, priority virus testing, food safety, patient engagement in care, etc.

· Targeted, culturally appropriate education on social distancing, face masks, and hand washing

· Mandated personal protection for essential service workers, e.g., custodial and clerical staff, mass transit operators, sanitation workers, food service workers; as well as testing for themselves and their families.

· Financial and insurance protection for uninsured workers

· Targeted testing in dense housing and other environments

· Support of local and state task forces to correct racial/ethnic COVID-19 disparities. Structuring targeted vaccination programs for all groups/ section of society once a COVID vaccine is developed

· Gathering more robust clinical data on COVID and these disparities [3,4,5]

ACUTE RENAL FAILURE

Acute renal failure (ARF) is, as the name implies, a rapidly progressive loss of renal function, generally characterized by oligourea (decreased urine production, quantified as less than 400 ml/day in adults [6], less than 0.5 ml/kg/h in children or less than 1ml/kg/h infants); body fluid disturbances; and electrolyte derangement [7].

CHRONIC RENAL FAILURE or END-STAGE RENAL DISEASE (ESRD)

Chronic Kidney Disease (CKD) means that the kidneys are damaged and losing their ability to keep one in healthy sate [2]. In the early stages of the disease, most people do not have symptoms. But as CKD gets worse, wastes can build up in your blood and make a person feel sick. Patients may develop other problems like high blood pressure, anemia, weak bones, poor nutritional health, and nerve damage. Because kidneys are vital to so many of the body's functions, CKD also increases the risk of having heart and blood vessel disease. While these problems may happen slowly and without symptoms, they can lead to kidney failure, which can appear without warning. Once kidneys fail, dialysis or a kidney transplant is needed to stay alive. The stage is reached when irreversible damage to nephrons is so severe that 75% of renal function has been lost and the kidney cannot function effectively. The two main causes of CKD are diabetes and high blood pressure. These two conditions were the primary diagnosis in 75% of kidney failure cases between 2015-2017. Other causes include glomerulonephritis (diseases that damage the kidney's filtering units), which are the third most common type of CKD; inherited diseases, such as polycystic kidney disease; malformations at birth that occur as a fetus develops; lupus and other immune diseases; obstructions such as kidney stones or an enlarged prostate; and repeated urinary tract infections & chronic pyelonephritis. The effects are a reduced filtration rate, selective reabsorption, secretion, and glomerular fibrosis which interfere with blood flow [8]. CRF is a progressive loss of renal function over a period of months or years through five stages. Each stage is a progression through an abnormally low and deteriorating glomerular filtration rate (GFR), which is usually determined indirectly by the creatinine level in blood serum. People with CKD are at greater risk for cardiovascular disease and death at all stages of CKD. CKD and heart disease are linked and have common risk factors, such as diabetes and hypertension. Each condition can lead to or worsen the other. An estimated 37 million American adults (1 in 7 adults; 15% of adults) are estimated to have CKD, but most don't know they have it. In fact, about 1 in 2 people with very low kidney function (not on dialysis) don't know they have CKD. Approximately

1 in 3 adults with diabetes and 1 in 5 adults with high blood pressure may have CKD. In 2017, 746,557 Americans had kidney failure, and needed dialysis or a kidney transplant to survive. Nearly 500,000 of these patients received dialysis at least 3 times per week to replace kidney function. Nearly 1,25,000 people started ESKD treatment in 2017, of which 120,834 started dialysis, and 20,945 received a kidney transplant. At the end of 2017, more than 222,848 Americans were living with a kidney transplant [2].

Signs and Symptoms:-

Initially it is without specific symptoms and can only be detected as an increase in serum creatinine or protein in the urine. However, as the function of kidney decreases, the following symptoms are encountered:-

· Blood pressure is increased due to fluid overload and production of vasoactive hormones leading to hypertension and congestive heart failure. (CHF)

· Urea accumulates, leading to azotemia and ultimately uremia (Symptoms ranging from lethargy to pericarditis and encephalopathy). Urea is excreted by sweating and crystallizes on skin (Uremic frost)

· Potassium accumulates in the blood (Known as hyperkalemia with symptoms ranging from malaise to fatal cardiac arrhythmias).

· Erythropoietin synthesis is decreased (Leading to anaemia causing fatigue).

· Fluid volume overload-symptoms may range from mild edema to life threatening pulmonary edema.

· Hyperphosphatemia-due to reduced phosphate excretion, associated with hypocalcaemia (due to vitamin D3 deficiency). Later this progress to tertiary hyperparathyroidism, with hypercalcaemia, renal osteo-dystrophy and vascular calcification.

· Metabolic acidosis, due to decreased excretion of acid by the kidney. This may cause altered enzyme activity by excess acid acting on enzymes and also increased excitability of cardiac and neuronal membranes by the promotion of hyperkalemia due to excess acid (Acidaemia) [9].

Diagnosis:-

It is important to differentiate CKD from acute renal failure (ARF) because ARF can be reversible. Abdominal ultrasound is commonly performed, in which the size of the kidneys are measured. Kidneys with CKD are usually smaller (< 9 cm) than normal kidneys with notable exceptions such as in diabetic nephropathy and polycystic kidney disease. Another diagnostic clue of CRF is a gradual rise in serum creatinine (over several months for years) as opposed to ARF in which a sudden increase in the serum creatinine (several days to weeks).

Stages of Chronic Kidney Disease (CKD)

All individuals with a Glomerular filtration rate (GFR) < 60ml/min./1.73 m2 for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage [2].

· Stage 1 CKD: - Slightly diminished function; kidney damage with normal or increased GFR (>90ml/min/1.73m2).

· Kidney damage is defined as pathological abnormalities or markers of damage, which include abnormalities in blood or urine and diagnosed by the test or imaging studies.

· Stage 2 CKD: - Mild reduction in GFR (<60-89 ml/min/1.73m2) with kidney damage.

· Stage 3 CKD: - Moderate reduction in GFR (<30-59ml/min./1.73m2).

· Stage 4 CKD: - Severe reduction in GFR (<15-29ml/min/1.73m2).

· Stage 5 CKD: - Established kidney failure (GFR < 15 ml/min./1.73m2; or permanent renal replacement therapy).[10].

Treatment:-

The best treatment of CKD is facilitated by early detection, when the disease can be slowed or stopped. Early treatment includes diet, exercise, medications, lifestyle changes, and treating risk factors like diabetes and hypertension. However, once kidneys fail, treatment with dialysis or a kidney transplant is needed. Control of blood pressure and treatment of the original disease, whenever feasible, are the broad principles of management. Generally, angiotensin converting enzyme inhibitors (ACEIs) or Angiotensin II receptor antagonists (ARBs) are used, as they have been found to slow the progression of CKD to stage 5 [11,12]. Replacement of erythropoietin and vitamin D3 two hormones processed by the kidney is usually necessary, as is calcium. Phosphate binders are used to control the serum phosphate levels, which are usually elevated in chronic kidney disease.

ETIOLOGY AND CLASSIFICATION OF RENAL DISORDERS

According to the western medicine a variety of etiological factors (like infection, nutritional, toxic and environmental) and pathogenic mechanism are involved in kidney disease. Many of these mechanisms are yet to be fully elucidated, thus it is difficult to precisely classify the kidney ailment [13,14]. The diseases and disorders of kidneys may be classified as Congenital and Acquired.

Congenital includes;

· Congenital malformations

· Congenital hydronephrosis

· Congenital obstruction of urinary tract

· Duplicated ureter

· Horseshoe kidney

· Polycystic kidney disease

· Renal dysplasia

· Unilateral small kidney

· Multicystic dysplastic kidney Parenchyma

· Cystic diseases of the Kidney:-

· Renal cystic dysplasia

· Polycystic kidney disease

· Glomerular cystic kidney disease

· Medullary cystic disease

· Simple renal cysts

- Acquired renal cysts
- Para renal cysts

Glomerular diseases

Primary glomerulonephritis:-

- Acute glomerulonephritis
- Rapid progressive glomerulonephritis
- Membranous glomerulonephritis
- Membrano-proliferative glomerulonephritis
- Focal glomerulonephritis

Tubular diseases

Acute tubular necrosis (ATN):-

- Ischaemic ATN
- Toxic ATN

Tubulointerstitial Diseases:-

- Acute pyelonephritis
- Chronic pyelonephritis
- Tuberculous pyelonephritis
- Myeloma nephropathy
- Nephrocalcinosis

Renal Vascular Disease:-

- Hypertensive vascular disease
- Thrombotic renal disease
- Renal cortical necrosis

Obstructive Uropathy:-

- Urolithiasis
- Hydronephrosis
- Unilateral hydronephrosis
- Bilateral hydronephrosis
- Tumours of the kidney

Benign tumour:-

- Cortical adenoma

Others:-

- Angiomyolipoma
- Mesoblastic nephroma
- Multi-cystic nephroma
- Juxtaglomerular tumour or (Reninoma)

Malignant tumours:-

- Adenocarcinoma of kidney (Renal cell carcinoma, Hyper-nephroma, Grawtiz tumour)
- Wilm's tumour (Nephroblastoma)

Other secondary tumours:

- The above disorders may leads to renal failure, which may be acute or chronic.

UNDESTANDING NEPHROTOXICITY

The definition of nephrotoxicity was chosen to be a change in creatinine clearance greater than 20% [15]. Any adverse functional or structural change in the kidney due to the effect of chemical or biological product, that is inhaled ingested or absorbed or which yields metabolite with an identifiable toxic effect on the kidney characterized as nephrotoxicity. By extension the concept of nephrotoxins is occasionally applied clinically to the renal effects of physiological substances circulating in abnormal concentration such as may occur in hypercalcemia, hyperuricaemia or hypokalemic nephrotoxicity [16].

Classification of nephrotoxic substances:

Class 1:Drugs or chemicals or their metabolites with a reasonable direct effect producing an identifiable morphologic or persisting functional change in the nephron.

Class II: Compounds producing sensitivity diseases identifiable as the nephritis or nephritic syndrome.

Class III: Compounds producing sensitivity reactions of the angitis or vasculitis including the kidney as the vascular organ.

Class IV:Compounds which may produce chronic nephrotoxicity where the mechanism extends over a period of months or years and evidence remains largely epidemiological or circumstantial.

Class V: Compounds, which aggravate pre-existing renal disease. [16].

NEPHROTOXINS

a) Metals Mercury, Bismuth, Uranium, Cadmium, Lead, Gold, Iron, Copper, Thallium and Antimony

b) Organic solvents Carbon tetrachloride, Tetrachloro ethylene, Methylcellulose, Methanol, Miscellaneous solvents.

c) Glycols Ethylene glycol, Ethylene glycol dinitrite, Propylene glycol, Ethylenedichloride and Diethyl glycol.

d) Physical agents Radiation, Heat Stroke, Electric shock

e) Diagnostic agents Contrast agents in high concentration

f) Therapeutic agents Sulphonamides, Penicillin, Streptomycin, Vanomycin, Bacitracin, Polymycin, Colestin, Neomycin, Tetracyclines, Amphotericin, Salicylates, Para Amino Salicylic Acid, Phenacetin, Pyenylbutazone, Phenindione, Puromycin, Tridione, Paradione.

g) Osmotic agents Sucrose

h) Insecticides Chlorinated hydrocarbons

i) Miscellaneous Carbon monoxide, Snake venom, Mushroom poisoning, spider venom,Chrysol, Beryllium.

j). Abnormal concentrations of physiologic substances hypercalcemia, hyperuricemia hypokalemia etc.

NEPHROTOXIC DRUGS

The usage of certain drugs in long run may lead to nephrotoxicity. The drugs tend to get accumulated in the form of by products which lead to renal failure or nephropathy. Some examples are as follows:-

Class	Drugs
Amino glycosides	Gentamicin, Amikacin, Tobramicin, Streptomicin
Anti-tubercular drugs	Streptomycin, Rifampicin, and Isoniazid
Penicillin	Ampicillin, Amoxicillin, Cloxacillin Carbenicillin, Penicillin
Tetracyclines	Tetracycline, Doxcycline
Sulphonamide	Cotrimoxazole, Sulphadizine
Anti-hypertensive drugs	Atenolol, Propanolol, Metopropolol Captopril, and Enalapril
Analgesic Sedative	Acetamenophene, Aspirin, Opioids analgesics Chlorodiazepoxide, Diazepam
Anti-gout and anti-arthritic	Allopurinol, Ibuprofen, Indomethacin, Naproxane, Piroxicam, Phenylbutazone
Anti-viral	Cyclophosphamide, cyclosporine, Malphalan, Vincristine, Azothioprim
Corticosteroids	Cortisone, Hydrocortisone, Prednisolone, Methyl prednisolone, Beta methasone, Triamcinolone
Urinary antiseptics	Cortisone, Hydrocortisone, Prednisolone, Methyl prednisolone, Beta methasone, Triamcinolone
Other drugs	Cisplatin, Phenytoin sodium, Lithium carbonate, phenoformin, Metformin, Amphotericin, Frusemide, Gold, Iodine contrast media, Triodone, Snake venom.

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