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Chronic Kidney Disease; Introduction, Causes, Complications and Diagnosis: A review

Yousoof Aasim[1], Mishra Kajal[2], Singh Rakendra[3], Patil R.K[4]

Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda[1]

Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda[2]

Department of General Medicine, Adesh Institute of Medical Sciences and Research, Adesh University[3]

Department of Pharmacy Practice, Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University[4]

ABSTRACT

Chronic kidney disease can be defined as decreased renal function for greater than 3 months. In terms of GFR, it can be defined as decreased glomerular filtration rate of < 60 ml/min/1.73m^2 . A GFR of < 60ml/min/1.73 m^2 is referred as decreased GFR and a GFR of < 15ml/min/1.73m^2 is referred as kidney failure. Albuminuria is the commonest marker of glomerular diseases such as diabetic glomerulosclerosis. Hypertension, diabetes, glomerulonephritis, PCKD, drugs, age is main risk factors predisposing chronic kidney disease. Among all these factors, diabetes is the most common risk factor leading to kidney disease. Patients with chronic kidney disease have lot of metabolic abnormalities such as water imbalance, electrolyte imbalance, uremia and hormonal imbalance. A number of assessments and tests are available for diagnosis of kidney disease such as measurement of GFR values, albuminuria, renal biopsy and radiological procedures. Due to rise in the prevalence and incidence of chronic kidney disease in last two decades, it has become a major worldwide health problem.

KEYWORDS- Chronic kidney disease, hypertension, GFR, diabetes, polycystic kidney disease (PCKD)

INTRODUCTION

The kidneys are bean-shaped organs with a centre concavity and lateral convexity. Male kidneys typically weigh between 150 and 200 g, whereas female kidneys typically weigh between 120 and 135 g. The measurements are typically 10 to 12 cm in length, 5 to 7 cm in width, and 3 to 5 cm in thickness. The size of each kidney is

comparable to a closed fist. They are situated between the transverse processes of T12 and L3 on the posterior abdominal wall, retroperitoneally [2]. Nephron is the structural and functional unit of kidneys. Nephron consists of glomeruli and tubules .The function of glomeruli is to filter wastes and excess fluids whereas tubules collect the waste to form urine. The kidneys are responsible for getting rid of waste products, drugs, and toxins through our urine. They also regulate electrolyte (salt) concentrations; help regulate blood pressure, maintenance of acid-base balance and production of hormones such as erythropoietin that affects blood [3]. Kidney function is evaluated by glomerular filtration rate (GFR). Renal clearance methods are used to measure GFR; the gold standard, inulin clearance, is difficult to measure. As a result, alternative approaches to calculating GFR have been used. The most common measurement is endogenous creatinine clearance (CrCl), however creatinine secretion inflates GFR [10]. In young adults normal GFR value is approximately 120 ml/min/1.73m^2 and this value gradually decreases with age. However decrease in GFR can also be indicative of decreased renal function which may be suggestive of kidney disease [16].Chronic kidney Disease results from decreased glomerular function for greater than three months. In terms of glomerular filtration rate, it is defined as decreased GFR of < 60ml/min/1.73m^2 present over 3 or greater than 3 months [42]. Due to the crucial role that GFR plays in the pathophysiology of complications, the disease is divided into five stages based on GFR: stage 1 is marked by a GFR of more than 90 mL/min/1.73m^2, stage 2 is marked by a GFR of 60-89 mL/min/1.73m^2, stage 3 is marked by a GFR of 30-59 mL/min/1.73m^2, stage 4 is marked by a GFR of 15 mL/min/1.73m^2 (stage 5) [5]. The main risk factors are age, gender, family history, ethnicity, low birth weight, obesity, socio-economic status, smoking, nephrotoxins, acute kidney injury, diabetes mellitus, hypertension etc [1]. CKD is linked to a number of unfavorable clinical outcomes, including death, cardiovascular events, kidney failure necessitating renal replacement treatment, and generalized low quality of life for survivors [11].Recent studies have shown that infections increase mortality in ESRD patients. Approximately 50% of mortality in CKD patients is related to non-cardiovascular causes of which infection is considered one of the causes. Cardiovascular disease and infections are jointly responsible for up to 70% of deaths in individuals with chronic kidney dysfunction because they are both directly or indirectly linked to altered immune response, which results in high incidence of morbidity and mortality [4]. Infections that occur during dialysis process contribute greatly to complications in CKD patients and also contribute to increased risk of death. Inappropriate drug prescribing is another major cause of increased risk of infections in CKD patients which lead to further complications. According to the global burden of illness project, the prevalence of CKD increased by 19.6% between 2005 and 2015, based on a sophisticated Bayesian model that combined data from numerous sources worldwide [12]. The rise in the prevalence of diabetes mellitus, hypertension, obesity, and ageing are the key factors contributing to this disease's global rise. However, in some areas, other factors like infection, herbal remedies, and environmental pollutants are still prevalent [12]. Due to rise in the prevalence and incidence of chronic kidney disease in recent decades, it poses a major threat to global healthcare system. According to WHO, the annual death rate is 850000-1000000 because of CKD. Chronic kidney disease is preventable and treatable and attention needs to be paid in making global health policies to tackle CKD.

CAUSES

HYPERTENSION

All individuals with newly diagnosed hypertension should be tested for CKD as a potential cause, and In order to halt the progression of CKD, hypertension must be treated [7]. Volume overload, sympathetic overactivity, salt retention, endothelial dysfunction, and changes in the hormonal systems that control blood pressure are some of the mechanisms causing hypertension in CKD. RAAS activity is more active when CKD is present. Peritubular capillaries downstream of sclerosed glomeruli have diminished blood flow. This decreased effective (perceived) blood flow causes the glomeruli in certain areas to oversecrete renin, which raises the levels of circulating angiotensin II. Direct vasoconstriction caused by angiotensin II raises blood pressure and systemic vascular resistance. Each remaining glomerulus in CKD must improve its glomerular filtration rate (GFR) because there are fewer working glomeruli; rising systemic arterial pressure supports both perfusion pressure and GFR [6]. The glomeruli are damaged, which causes an increase in protein filtration and unusually high levels of protein in the urine (microalbuminuria or proteinuria). Microalbuminuria, which manifests as minute levels of albumin in the urine, is frequently the initial indication of CKD. As CKD worsens, proteinuria (protein-to-creatinine ratio 200 mg/g) develops, which is linked to a poor prognosis for kidney disease as well as CVD [14].

DIABETES

High blood sugar levels caused by inadequate insulin synthesis or problems with insulin function in the body are a hallmark of diabetes. About 90 to 95 percent of cases of diabetes are type 2 (also known as noninsulin-dependent diabetes), which is significantly more prevalent than type 1 (insulin-dependent diabetes). Although type 2 diabetes is more prevalent in persons over 40, it is also becoming more prevalent in younger generations, including children and teenagers. (Kidney.org). After a mean of 15 years with type 1 DM, 20 to 30 percent of individuals will have microalbuminuria, and less than half of these patients will advance to microalbuminuria, also known as overt nephropathy. The majority of patients will advance to end-stage renal disease (ESRD) after overt nephropathy develops, with reported rates of 4% to 17% at 20 years and roughly 16% at 30 years from the time of initial DM diagnosis [17].

High glucose levels hinder cell development, growth factor production, and gene occurrence, all of which contribute to an increase in extracellular matrix. Cell harm could result from hazardous chemicals that hyperglycemia may produce. TGF, for instance, is one of these harmful substances. The glomerular mesangium produces more extracellular matrix as a result of TGF. Additionally, decreased extracellular matrix clearance is brought on by collagenase inhibition. A prolonged hyperglycemia's metabolic impacts include the development of advanced glycosylated end products (AGE). Some of the extra glucose in hyperglycemia attaches to amino acids in blood or tissue proteins, which eventually causes the creation of

AGE. AGE then binds to collagen and causes microvascular difficulties as well as renal issues [20]. Some proteins undergo structural modifications as a result of long-term hyperglycemia, and these new molecules have a high biological activity, such as HbA1c.According to studies, AGE-containing proteins boost protein kinase C activity and the production of TGF. Apoptosis, cell differentiation, and cell proliferation are all significantly influenced by protein kinase C. This enzyme boosts the production of endothelin, cytokines, and extracellular matrix. As a result of these modifications, the glomerular basement membrane thickens, arteries become blocked, and glomerular permeability increases.

Aldose reductase is yet another crucial enzyme in the pathophysiology of diabetic nephropathy. Glucose is converted to sorbitol by this enzyme. Long-term hyperglycemia raises sorbitol synthesis and enzyme activity, which raises extracellular matrix. Mesangium volume and thickening are increased by extracellular matrix buildup in the glomerular basement membrane (GBM) [21].

Increased blood glucose levels in diabetic patients over time leads to combination of glucose with proteins and lipids through the process of non enzymatic glycation. This results in release of pro inflammatory molecules which attack the efferent arteriole causing inflammation and finally lead to arteriosclerosis. Arteriosclerosis can be either hyaline (due to protein and lipid deposition) or atherosclerosis (plaque deposition in efferent arteriole). Due to thickening of walls of efferent arteriole blood flow is reduced which results in increased back pressure in glomerulus. This leads to increase in GFR for a time being. Due to increased GFR, the mesangial cells surrounding glomerulus sense the increased filtration rate and lead to release of TGF- beta which leads to fibrosis around the glomerulus resulting in glomerulosclerosis which finally leads to decrease in GFR. Secondly, the inflamed efferent arteriole leads to decreased oxygen supply to the surrounding tubules which may result in tubular disease contributing to decreased GFR [5].

GLOMERULONEPHRITIS

The term "glomerulonephritis" refers to a group of conditions marked by inflammatory changes in the glomerular capillaries and accompanying signs and symptoms of an acute nephritic syndrome, particularly haematuria, proteinuria, and diminished renal function in some cases linked to fluid retention, hypertension, and edema [23]..Glomerulonephritis is another factor leading to decrease in GFR. A number of causes can lead to glomerulonephritis such as infections, autoimmune disease, HIV, rheumatoid arthritis etc. Glomerulonephritis can be caused by a variety of triggers both endogenous and external, such as medicines and viral agents as well as cancer, autoimmune, and ultrastructural abnormalities of the kidney, can cause glomerulonephritis. Second, there is individual variation in glomerulonephritis susceptibility, which presumably has a genetic foundation. For instance, only a small percentage of people with hepatitis C virus infection get glomerulonephritis. Third, intricate interactions between cells (both leucocytes and intrinsic kidney cells) and soluble substances (such as antibodies, complement, chemokines, cytokines, and growth factors) mediate glomerular inflammation [26].

POLYCYSTIC KIDNEY DISEASE

Multiple fluid-filled cysts are seen in the kidneys of people with polycystic kidney disease (PKD), while other organs may also be impacted. Although PKD is monogenically inherited, it is heterogeneous in terms of phenotype, genetic makeup, and allelic makeup. The most prevalent kind of PKD, autosomal dominant polycystic kidney disease (ADPKD), is characterized by slowly growing renal cysts that begin to form in gestation and can come from anywhere in the kidneys, though they typically form in the distal portions of the nephron and the collecting duct [28]. Approximately 5% of people with ESRD have polycystic kidney disease (PKD), the fourth most common cause of renal failure in the country. Approximately 25% of patients who begin dialysis undergo a transplant in the first year following dialysis, which is higher than the 5% transplant rate for the whole incident US ESRD population. On the other hand, mortality in the first year is lower, at 6% versus 24% for the overall ESRD group. [29].

Due to presence of cysts at various parts of nephron, compression of renal vessels occur which leads to reduction of oxygen delivery to the renal tubular cells affecting the processes of tubular reabsorption, tubular secretion of substances. Reduction in oxygen delivery also causes ischemia in the tubular cells which may precipitate necrosis of tubular cells. The compression effect of cysts in PCKD can also cause reduction in blood flow through kidney tubules which lead to reduction in GFR. Due to decreased GFR, JG cells of kidney secrete rennin which activates RAAS system causing increase in BP. Increased blood pressure over prolonged period leads to glomerulosclerosis and further decrease in GFR as discussed earlier. This type of hypertension is called as secondary hypertension.

DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs), which include analgesics, are among the most widely used prescription and over-the-counter (OTC) treatments worldwide. NSAIDs have long been known to cause kidney damage. There is conflicting information about the long-term effects of chronic NSAID usage on renal function, with some studies indicating a dose-response impact and others showing a risk increase of two to eight times for renal deterioration or hospitalisation for acute kidney damage [30] Many medications have the potential to cause AKI and CKD, frequently by inducing interstitial nephritis. Penicillins, non-steroidal anti-inflammatory medicines (NSAIDs), proton pump inhibitors, diuretics, and anti-retrovirals are medications linked to acute interstitial nephritis. [7].

Lithium therapy administered over an extended period of time may result in nephrogenic diabetic insipidus and an interstitial nephritis. Occasionally, medications like penicillamine and gold might result in glomerulonephritis [7]..

Prolonged use of NSAIDs can result in reduction in GFR by mechanisms involving inhibition of prostaglandins PGI_2/PGE_2. Prostaglandins are vasodialatory substances which maintain normal blood flow in afferent and efferent arterioles, thus maintaining normal GFR. Overuse of NSAIDs can lead to inhibition of PGI2/ PGE_2 therefore limiting their vasodialatory effects. Inhibition of these prostaglandins causes vasoconstriction and decreased glomerular blood flow and a reduction in GFR.

CLINICAL MANIFESTATIONS

1. **Electrolyte imbalance**

The ability to defend against sodium overload and salt depletion is lost in CKD stages 4 to 5, and perhaps in CKD stage 3. In addition to edema, which may have a detrimental impact on one's quality of life, excess salt and fluid also contribute to hypertension and subsequently CVD (more specifically, concentric left ventricular hypertrophy, which may cause diastolic dysfunction) [4]. Patients with low GFR have reduced ability to filtrate potassium and phosphate in the urine. This leads to increased potassium and phosphate levels in the body resulting in hyperkalemia and hyperphosphatemia. The potential danger of arrhythmias linked to poor cardiac outcomes and a rise in mortality rates makes hyperkalemia one of the most significant. The progressive adaptation of the serum potassium-concentration regulation systems enables the kidneys to maintain potassium homeostasis over the long term despite declines in glomerular filtration rate (GFR) associated with the progression of CKD [33]. Nutritional needs change when GFR declines. Periodically evaluating nutritional status is recommended. For CKD stages 1 through 5, low-protein diets are advantageous, however nutritional control should be done so as not to jeopardize nutritional status. Patients on maintenance dialysis need to have a high protein diet in order to maintain adequate nutritional status [34].

2. **Water imbalance**

Due to low GFR most of the water is retained in the body. In tissues and organs there is increased water retention leading to different types of edema such as pulmonary edema, peripheral edema and hypertension. Excess fluid volume with salt retention, increased renin-angiotensin activity, and increased sympathetic nerve activity all contribute to hypertension in CKD. Endothelium-mediated vasodilatation decreased nitric oxide production, and therapy with erythropoietin for secondary hyperparathyroidism. Lastly, hypertension either directly causes or indirectly facilitates the development of CKD ([35] Kidney damage also presents with excretion of most of the albumin in the urine. Albumin concentration falls in the blood. As albumin is essential to maintain osmotic gradient in the vessels, water loss occurs into the interstitial fluid which exaggerates pulmonary and peripheral edema [15].

3. **Uremia**

The accumulation of organic waste products that the kidneys ordinarily remove is thought to be a major cause of uremic disease [36].In people with kidney damage, urea starts to build up in the blood leading to initial signs of azotemia which may precipitate uremia. Urea build up in the body can cause many complications such as seizures, encephalopathy, asterexis and even coma. Apart from these complications urea build up in the body can also cause uremic pericarditis. In the skin urea build up usually presents with uremic frost. The other complication is that of increased risk of bleeding as urea also affects platelet aggregation. So in patients with kidney damage, there is increased risk of bleeding. Protein-bound uremic toxins are thought to be one of the CKD-specific non-traditional risk factors and to play a significant role in the development of cardio

renal syndrome based on the association between serum concentrations of these toxins and the incidence of CVD and mortality in patients with CKD. Numerous investigations showed that leukocytes, such as monocytes and macrophages, smooth muscle cells, and vascular endothelial cells are all seriously harmed by protein-bound uremic toxins [37].

4. Hormonal imbalance

Kidney cells make a hormone called erythropoietin which is essential for the process of erythropoiesis. Hypoxia initiates erythropoiesis, which is tightly controlled by hormones, growth factors, cytokines, and vitamins to guarantee appropriate oxygen delivery to all body cells. Different types of anaemia necessitating various therapies may be caused by abnormalities in one or more of these variables. Erythropoietin is a crucial component in the synthesis of red blood cells. It is a glycoprotein hormone, primarily produced by the kidneys, that stimulates erythroid progenitor cell survival and differentiation in the bone marrow and controls iron metabolism. The normochromic normocytic anaemia that is frequently seen in individuals with advanced chronic renal disease is primarily caused by a deficiency in erythropoietin production [38].Due to damaged kidneys or kidney dysfunction erythropoiesis is also affected which can result in anemia. This type of anemia is called as anemia of chronic disease. The other thing is that decreased g.f.r. is sometimes sensed by JG cells of kidney as decrease in blood pressure. This leads to release of rennin and activation of RAAS system causing increase in blood pressure or secondary hypertension. Also due to decreased calcium absorption in the gut as discussed earlier, parathyroid hormone sense hypocalcaemia and draws calcium from bones which can have serious effects in elderly patients such as patients may present with fractures, renal osteodystrophy and osteitis fibrosa cystic (OFC) due to excessive production of PTH [40].

5. Metabolic acidosis

Maintaining acid-base balance is mostly the responsibility of the kidney. As a result, in the course of chronic kidney disease, a fall in serum bicarbonate concentration and a decrease in renal ammonium excretion are seen [41]. Acidosis has been linked to higher mortality, bone disease, hypoalbuminemia, inflammation, and muscle atrophy. Base administration may lessen muscular atrophy, enhance bone disease, and halt the course of CKD [41].When kidneys are damaged its bicarbonate ($HCO3^-$) reabsorption capacity is decreased and potentiate proton (H^+) excretion capacity is also decreased leading to reduction in pH and metabolic acidosis. The development of metabolic acidosis in CKD is caused by the kidneys' inability to eliminate the acid load, which results in a positive H+ balance and low tCO2 concentration. Normally, the metabolism of food components to H+ and base determines a major portion of the daily acid load [42]

6. Hyperlipidemia

Patients with chronic renal disease frequently have dyslipidemia. The causes change depending on the stage of the kidney condition, the level of proteinuria, and the method used to treat end-stage renal disease. Dyslipidemia have been linked to the advancement of renal disease [44]. Dyslipidemia linked to chronic renal impairment is brought on by a number of reasons. The activity of hepatic triglyceride lipase and lipoprotein lipase is decreased in CKD patients. As a result, the circulation of these atherogenic lipoproteins is increased. This prevents the liver and peripheral tissue from absorbing triglyceride- and apolipoprotein B-rich lipoproteins. It is believed that increased lipoprotein synthesis and impaired lipoprotein catabolism cause hypercholesterolemia in nephrotic syndrome [13]. Patients with chronic kidney disease have less albumin concentration in the blood. Liver stimulates the production of albumin along with other proteins such as lipoproteins ad triglycerides which can lead to hyperlipidemia.

DIAGNOSIS

The first thing that gives an idea about the presence of chronic kidney disease is the time period for which there is reduced GFR of < 60ml/min/1.73m^2. Normally a decreased g.f.r of < 60 consistently for more than three months is evident of renal disease [4]. The following assessment parameters are useful and usually employed for diagnosis and estimation of kidney damage:

GFR: The renal clearance of exogenous filtration markers can be used to indirectly quantify GFR. Inulin is the marker for the reference standard. Because inulin is inert, does not interact with plasma proteins, passes through the kidneys easily, and does not undergo metabolism, tubular secretion, or reabsorption, it is quickly eliminated into the urine through glomerular filtration [45]. Due to its inconvenience and high cost, inulin is rarely utilised in practise; instead, other filtration markers are used [45]. Based on g.f.r. values, National Kidney Foundation and KDOQI has classified CKD into following stages (Kidney international supplements). Creatinine and cystatin C are frequent biomarkers used to calculate GFR, and the majority of pathology services do eGFR tests regularly. The main drawback of using biomarkers is that their measured concentrations are subject to variations due to factors other than variations in GFR [45], [4].

Albuminuria: albuminuria is strongly associated with the risk of CKD progression in patients having diabetic and cardiovascular comorbidities. Proteinuria is the most powerful predictor of ESRD [5].The severity of kidney disease is strongly correlated with albuminuria (MDRD& AASK). One of the tests for detection of severity of kidney disease is urine albumin: creatinine ratio (ACR) Based on this, CKD can be classified as

SEVERITY	ACR
Mild	< 30
Moderate(micro)	30-299
Severe (macro)	≥ 300

Radiological Assessment: Number of radiological tests and procedures are employed to evaluate patients with renal disease. A single test or a number of tests can be performed for detection, diagnosis and/or evaluation of multiple conditions associated with kidney disease [47].These tests are more often used to determine urinary tract obstruction, renal cyst, kidney stones ,size of kidneys, renal vascular disease etc. Ultrasonographies, MRI, CT are most commonly employed radiological tests carried out for early diagnosis of chronic kidney disease.

Renal biopsy: Renal biopsy is proven to be safe and effective to achieve a correct diagnosis of kidney disease regardless of age and glomerular filtration rates. The main histological presentations are primary and secondary glomerulonephritis. Hematuria, albuminuria and changes in kidney function are the main parameters detected in renal biopsy. Kidney tissue sample in renal biopsy can be evident of scarring, inflammation, infection or unusual deposits of immunoglobulin. A renal biopsy can also highlight the progression of kidney disease. In elderly population, renal biopsy resulted in change of therapy in 40% patients according to findings from various studies [4].

Serology: Possible serological tests for detection of CKD include following

- Antinuclear antibody + RF
- Antineutrophil cytoplasmic antibody (ANCA)
- Hepatitis B & Hepatitis C virus studies
- Anti glomerular basement membrane antibody
- HIV

CONCLUSION

Chronic kidney disease is a major health problem affecting millions of people worldwide. A rising financial burden for treatment of CKD has increased in last two decades. Most of the affected people are not aware of their symptoms until kidney function deteriorates and GFR decreases to very low levels. Better understanding of the pathophysiological changes and warning signs and symptoms can help in early diagnosis of the disease and may help to reduce mortality in affected individuals. The causative factors of kidney disease need to be communicated with the people who are at high risk of developing kidney disease and there is also a need for addressing kidney related health issues.

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