Scientific Research Publishing

Open Journal of Nephrology, 2023, 13, 280-291
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Complexity and Management of Chronic Kidney Disease

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How to cite this paper: Wandile, P.M. (2023) Complexity and Management of Chronic Kidney Disease. *Open Journal of Nephrology*, **13**, 280-291.
https://doi.org/10.4236/ojneph.2023.133027

Received: August 23, 2023
Accepted: September 18, 2023
Published: September 21, 2023

Abstract

Chronic Kidney Disease (CKD) is ongoing damage of the kidneys, which affects their ability to filter the blood the way they should. Worldwide CKD is considered as the 16th leading cause of death and affects 8% - 16% of the population. CKD often goes unnoticed and is revealed as an incidental finding. Healthcare providers diagnose the condition as CKD based on persistent abnormal kidney function tests revealing kidney damage markers > 3 months, urine albumin creatinine ratio (UACR) > or equal to 30 mg/g per 24 hours, and GFR < 60 mL/min/1.73m^2. In this article, we have discussed chronic kidney disease in terms of kidney physiology, chronic kidney disease pathophysiology, etiology, diagnosis, signs and symptoms, and management.

Keywords

Chronic Kidney Disease, Stages of Chronic Kidney Disease, Diagnosis of Chronic Kidney Disease, Chronic Kidney Disease Management, Physiology of Kidneys, Pathophysiology of Kidneys, Renal Replacement Therapy

1. Introduction

Healthcare providers diagnose the condition as CKD based on the persistent abnormal kidney function tests which reveal kidney damage markers > 3 months or UACR > or equal to 30 mg per 24 hours, GFR < 60 mL/min/1.73m^2, UACR > or equal to 30 mg/g or kidney damage or renal tubular disorders showed up in kidneys histology or imaging testing. Failing kidneys are unable to excrete excess fluid and waste from the blood, and it remains in the body, leading to associated medical conditions such as cardiovascular complications, stroke, ESRD, and death. One of the chief causes of CKD is diabetes, which is recognized as a lifestyle, metabolic, and autoimmune disorder that leads to microvascular complications, fatty deposition inside the blood vessels, leading to blockages, and

hypertension. Another significant cause of CKD is hypertension. Hypertension is not just the cause of CKD, but it is also one of the complications of CKD. Hence, healthy life choices such as exercise, healthy diet, and weight reduction had paramount importance in halting the progression of CKD. CKD complications include anemia, metabolic disorders such as metabolic acidosis, fluid overload, secondary hyperparathyroidism, hypercalcemia, Vitamin D deficiency, hyperkalemia, and hyperphosphatemia [1] [2].

2. Discussion

2.1. Physiology of Kidneys

The kidneys are vital organs responsible for maintaining a wide range of physiologic functions in the body. Their primary role is to filter and excrete waste products and excess substances from the blood circulation, regulate fluid and electrolyte balance, control blood pressure, and produce hormones that influence various bodily processes.

The nephron is the functional unit of the kidney, and it consists of renal tubules and glomerulus. The glomerulus is a network of capillaries that filter blood. As blood flows through the glomerulus, small molecules like water, electrolytes, and waste products are removed from the blood into renal tubules, forming a fluid called filtrate. The glomerular filtration rate is the rate at which the filtration occurs. As the filtrate flows through the renal tubules, essential substances like glucose, amino acids, and electrolytes are reabsorbed back into the bloodstream. This process ensures that the body retains important nutrients while eliminating waste products. In addition to filtration and reabsorption, the renal tubules also secrete certain substances into the filtration. This process allows the kidneys to control the levels of specific ions and waste products in the body. In response to reduced oxygen levels in the blood, kidneys produce erythropoietin-stimulating hormone (EPO) which stimulates the bone marrow to increase red blood cell production. In response to low blood pressure or low sodium in the blood, specialized cells in the kidneys secrete Renin, which initiates rennin-angiotensin-aldosterone system (RAAS), it helps to balance blood pressure and fluid in the system. Kidneys convert Vitamin D into its active form called calcitriol which is essential for the absorption of calcium and phosphate in the intestines, aiding in bone health. Kidneys play a crucial role in regulating blood pressure by adjusting blood volume and the constriction or dilation of blood vessels through rennin-angiotensin-aldosterone system and secreting atrial natriuretic peptide hormone (ANP) in the case of increased blood volume. Kidneys maintain a delicate balance of fluids and electrolytes such as sodium, potassium, and calcium in the body. This balance is essential for overall health and is achieved through the reabsorption and excretion of these substances. Kidneys help to regulate the body's pH by reabsorbing bicarbonate ions and secreting hydrogen ions as needed to maintain a stable blood pH level. The kidneys filter out waste products, toxins, drugs, and metabolic byproducts from the

bloodstream, which are then excreted in the urine. This detoxification process is critical for maintaining the body's internal environment. The filtrate that has undergone reabsorption and secretion processes in the renal tubules is finally converted into urine. Urine is then transported from the kidneys to the bladder for storage and eventual elimination from the body. The kidneys play a central role in maintaining homeostasis in the body, regulating a wide range of physiological processes critical for health and well-being. Dysfunction or disease of the kidneys can lead to various health problems and disruptions in these vital functions [3] [4].

2.2. Pathophysiology of Chronic Kidney Disease

Chronic kidney disease is manifested by progressive, gradual loss of kidney function. The pathophysiology of CKD involves a series of complex and interconnected processes, and it includes the following key components.

Underlying conditions or events that damage the kidneys such as hypertension, diabetes mellitus type I and II, genetic kidney disorders, glomerulonephritis, and systemic infections. In many cases, the initial injury to the kidneys leads to narrowing or damaging renal blood vessels causing renal hypoperfusion and ischemia. Kidney injury triggers an inflammatory response, secreting pro-inflammatory agents and causing further kidney tissue damage. Oxidative stress occurs when there is a lack of balance between the production of reactive oxygen species and the ability of the body to neutralize them. Inflammation and reduced blood flow can cause oxidative stress and damage kidney cells and proteins. Repeated episodes of injury and repair can lead to fibrosis in the kidneys. This fibrosis disrupts the normal structure and function of renal tissue, impairing the kidney's ability to filter waste products and maintain fluid and electrolyte balance. Damage to the glomeruli can result in proteinuria and impaired filtration of waste products. This can lead to edema and electrolyte imbalances. The renal tubules, responsible for reabsorbing essential substances and excreting waste products, can also be affected. Tubular dysfunction can result in abnormalities in electrolyte and acid-base balance. As the kidney function declines, the body's ability to regulate blood pressure and fluid balance is compromised. This can lead to hypertension and fluid overload, which further strains the kidneys [5] [6].

2.3. CKD Etiology

CKD causes consist of polycystic kidney disease, diabetes, hypertension, autoimmune disorders, malignancy, chronic infections, genetic disorders, environmental exposures such as nephrotoxins, certain drugs, antibiotics, chemotherapy infection, and glomerulonephritis [2]. Risk factors consist of obesity and certain genetic causes such as sickle cell trait and systemic lupus erythematosus (SLE) etc. Certain races are more prone to CKD as compared to others, such as African Americans and Pacific Islanders, due to the genetic tendency toward diabetes,

hypertension, and obesity. Genetic factors such as 2 APOL1 risk alleles carry > two-time risk of CKD and up to a 29-times greater risk of certain CKD diseases such as focal-segmental glomerulosclerosis compared to those who carry 0 or 1 risk allele. Sickle cell traits have two times increased risk of CKD [7] [8] [9] [10] [11]. CKD progression can cause several complications leading to ESRD and death [12] [13] [14] [15].

Therefore, CKD screening is suggested in this patient group in addition to the patients who have a history of acute kidney injury, obesity, recurrent urinary tract infections, kidney stones, reduced kidney mass, certain medications NSAID, and lithium. Confirming the cause of CKD is crucial for the treatment and prognosis [16] [17].

2.4. Diagnosis of CKD

Rule out CKD from acute kidney injury and acute kidney disease [2] [18]. Patients could present with symptoms such as flank pain, reduced urinary output, hematuria, foamy urine, nocturia, or enlarged kidney, which requires ruling out; pyelonephritis, polycystic kidney disease, obstructive uropathy, nephrolithiasis, urinary hesitancy, urgency along with urinary obstruction, hemoptysis, lymphadenopathy, hearing loss, retinopathy, neuropathy, acute interstitial nephritis, vasculitis, fabry disease, scleroderma, palpable purpura, butterfly rash as seen in systemic lupus erythematosus [19]. Kidney ultrasound can be used for the diagnosis of CKD as it assesses morphology and rules out urinary obstruction [1].

In the case of advanced CKD, patients may be present with dyspnea, malnutrition, fatigue, peripheral edema, altered mental status, nausea, vomiting, diarrhea, unintentional weight loss, platelet dysfunction along with a tendency to bleed, peripheral neuropathy, anorexia, restless leg syndrome, erectile dysfunction, decreased libido, amenorrhea, symptoms of uremia.

Physical examination could reveal pericarditis, volume overload due to nephrotic syndrome, decompensated heart failure, or liver failure. Volume depletion could be caused by vomiting, diarrhea, poor oral intake, or due to over-diuresis. Vascular complications could be presented with carotid or abdominal bruits, retinopathy could be present due to long-standing hypertension or diabetes, and neuropathy could be present due to diabetes rather than vasculitis or amyloidosis. The cause of CKD and risk factors need to be ruled out.

2.5. CKD Stages

The stages of CKD are determined by GFR, albuminuria, and etiology.

Typically, the value of serum creatinine and Cystatin C is used for the EGFR calculation.

The following formula is commonly used to provide more accuracy.

CKD-EPI 2009 creatinine equation.

CKD-EPI creatinine 2012—cystatin C equation.

In case of a change of creatinine metabolism such as a high protein diet, sig-

nificant high and low body mass affects renal excretion of creatinine. Cystatin C--based eGFR calculation is considered as the most suitable equation [2] [18] [20]. However, the correlation of elevated cystatin C levels with obesity, diabetes, and inflammation has been reported as well [20] [21].

Succeeding are five stages of CKD and the associated range of GFR [22]:

Stage 1 CKD GFR is normal or >90 mL/min/1.73m^2;

Stage 2 CKD is considered mild, GFR is 60 - 89 mL/min/1.73m^2;

Stage 3 A is considered moderate CKD, GFR is 45 - 59 mL/min/1.73m^2;

Stage 3B is considered moderate CKD, GFR is 30 - 44 mL/min/1.73m^2;

Stage 4 is considered severe CKD, GFR is 15 - 29 mL/min/1.73m^2;

Stage 5 is considered end Stage CKD, GFR is < than 15 mL/min/1.73m^2 [22].

Chronic kidney disease classification based on albuminuria.

Urinary albumin is considered the more specific and sensitive biomarker for glomerular pathology therefore, the value of urine albumin creatinine ratio (UACR) is recommended rather than urine protein creatinine ratio [2] [23].

CKD stages are based on UACR value.

Stage A1 CKD: UACR is less than 30 mg/g;

Stage A2 CKD: UACR is between 30 - 300 mg/g;

Stage A3 CKD: UACR is greater than 300 mg/g^2.

The first-morning urine sample is considered the preferable sample to test UACR as albumin, excretion in the urine differs over the course of the day [2] [24] [25].

2.6. Managing CKD

Management of Hypertension and Diabetes medicinal treatment approach.

1) For CKD patients having Diabetes and UACR > 30 mg per 24 hours. Or CKD patients who don't have diabetes and have UACR > 300 mg per 24 hours, the medicinal treatment advised is RASSi therapies. Dual therapy could lead to hyperkalemia and acute kidney injury therefore, it should be avoided [1] [26] [27] [28]. Hypoglycemic drugs are adjusted per the need. Achieving Glycemic control with a target of hemoglobin A1 c around 7.0% may reduce the progression of CKD [29] [30] [31].

2) For CKD patients with persistent hypertension, albuminuria, or heart failure with reduced ejection fraction, the medicinal treatments advised are aldosterone receptor antagonists, and for patients with severe albuminuria, SGLT-2 inhibitors-specific medication classes are recommended [27] [32] [33] [34] [35] [36]. Several research studies indicated that CKD patients with lower levels of albuminuria could also receive cardiovascular benefits from these classes of medications [37] [38].

3) Reducing the risk of cardiovascular disease

There is a high prevalence of cardiovascular disease among CKD patients as compared to non-CKD patients, therefore, cardiovascular risk management is crucial. Healthy life choices such as calorie control, exercise, weight reduction, more intake of fruits and vegetables, reduction of meat and fatty food intake,

and smoking cessation are recommended. Low to moderate dose Statin is indicated for 50 plus CKD patients irrespective of their low-density lipoprotein cholesterol level [39] [40] [41]. Eight joint National Committee and Kidney Disease guidelines suggested the goal of having blood pressure less than 140/90 in CKD patients [2] [42]. For patients having UACR > 30 mg per 24 hours the recommended blood pressure is less than 130 and 80 mm Hg [1]. NSAID is not recommended for CKD patients who are ACE/ARB users. Herbal supplements containing aristolochic acid and anthraquinone are suggested to cause kidney cancer, acute tubular necrosis, nephrolithiasis, and acute and chronic interstitial nephritis [42] [43]. Proton pump inhibitors are suggested to cause acute interstitial nephritis [44] [45] [46]. Phosphate-based bowel preparation has been reported to cause acute phosphate nephropathy [47] [48]. Therefore these agents should be avoided.

2.7. CKD and Its Complications' Management

The frequency of laboratory abnormalities depends on the stage of CKD. The lab testing could consist of a comprehensive metabolic panel, lipid profile, T3, T4, TSH, complete blood count, parathyroid hormone, 25—hydroxyvitamin D [1] [49] [50]. Monitor CKD patients for the development of renal complications such as anemia, electrolyte abnormalities, metabolic disorders, and mineral and bone disorders [1]. The anemia of CKD is the most common complication; depending on the complete blood count and iron test results oral and intravenous iron supplementation can be started: refractory persistent hemoglobin level, less than 10 g/dL directed toward erythropoietin stimulating agents' administration. The most severe adverse effects of ESA are a significant risk of thrombotic events, particularly in surgical patients, increased risk of ischemic stroke and myocardial infarction, and increased risk of venous thromboembolism [51].

Mineral, bone, and electrolyte abnormalities are common in CKD patients. It is suggested that concomitant Vitamin D deficiency, hypocalcemia, hyperkalemia, and hyperphosphatemia have been provided with adequate elemental calcium and vitamin D intake, low-potassium, and low-phosphorus diets [2] [26] [51] [52]. Metabolic acidosis is one of the complications of rapid CKD progression in patients with persistent low sodium bicarbonate value, treated with oral bicarbonate supplementation [2] [20] [53] [54] [55] [56].

2.8. Monitoring of CKD Progression

Free online help can help patients track their kidney health and CKD status and identify individuals who are the risk of CKD progression. It has been found that for CKD patients the need for prospective renal replacement therapy is very low [57]. Free online Kidney Failure Risk Evaluation Equation is available at https://kidneyfailurerisk.com/. It forecasts dialysis or transplant requirements of CKD patients in the next 2 - 5 years, especially for those patients who have eGFR < 60 mL/min/1.73m [1] [20] [58]. The equation is based on ba-

sic lab values for CKD patients, and it has been validated in more than 30 countries with more than 700,000 people. Another free online equation, CKD G4 + risk calculator is available at https://kidneyfailurerisk.com/ for patients with eGFR < 30 mL/min/1.73m^2. This estimator could forecast the cardiovascular disease risk and death [59] [60].

2.9. Nephrology Intervention

The following criteria require Nephrology evaluation and interventions. Signs and symptoms of nephrotic syndrome, <20 red blood cells in urine microscopy examination; patients having > 2200 mg per 24 hours of albuminuria, uncontrolled hypertension in CKD patients with several ongoing antihypertensive medications, glomerulonephritis signs and symptoms, ongoing hypokalemia or hyperkalemia, ongoing anemia requiring erythropoietin administration, to rule out if the patient has genetic renal disease, recurrent severe kidney stones, the unexplained ongoing decline in eGFR > 5 mL/min/1.73m^2 or speedy decline in eGFR > or equal to 25% from baseline [1], unsolved persistent albuminuria or increased albuminuria.

Kidney biopsy is indicated if the microscopic urine examination shows dysmorphic red blood cells or cellular casts or increased UACR along with a swift decline in GFR [2] [10] [58]. Kidney conditions and certain autoimmune conditions that can lead to ESRD are lupus, alport syndrome, polycystic kidney disease (PKD), interstitial nephritis, pyelonephritis, diabetic nephropathy, hypertension, glomerulonephritis, long-term use of certain medicines, narrowed or blocked renal artery, genetic renal disease [2] [10] [28] [53]. Evaluation of detailed diagnostic testing decides if kidney replacement therapy is needed. In certain emergency situations that lead to uremia, dialysis treatment is indicated right away.

Signs and symptoms of Uremia.

Nausea, vomiting, metallic taste in the mouth, fatigue, loss of appetite, frequent urination, cognitive dysfunction, muscle cramping, feet and ankles swelling, shortness of breath from fluid accumulation, dry and itchy skin, unexplained weight loss, In severe instances, symptoms of uremic fetor and uremic frost. Treatment for ESKD includes peritoneal dialysis, home hemodialysis, in-center hemodialysis, renal transplant, and conservative care without dialysis [60]. Peritoneal dialysis is not a good choice for patients with a history of abdominal scars related to multiple abdominal surgeries and unstable housing [23] [61] [62]. The hemodialysis treatment schedule could cause an inconvenience to the patients as patients have to travel to a dialysis center 2 - 3 three times a week. In addition, dialysis access carries the risk of infection. In old patients with reduced functional status, initiating dialysis was found to be related to a faster functional decline and increased short-term mortality [63] [64].

Kidney transplant surgery includes risks such as infection, injury to surrounding organs, bleeding, or death. According to KDOQI guidelines, an eGFR value between 15 - 20 mL/min/1.73 prompts dialysis treatment access creation.

A multidisciplinary approach is followed while initiating and managing renal replacement. Social workers discuss the patient's finances, and transportation arrangements with the patients, dieticians advise dietary regimens, nephrologists and dialysis nurses are involved in educating patients about their health and various treatment options. Patient preference needs to be considered in the treatment approach. Even though dialysis treatment is efficacious in reducing the mortality and morbidity of ESRD patients, living donor kidney transplants done before or immediately after dialysis treatment initiation are considered ideal treatment due to the best results it provides [65].

3. Conclusion

The ideal treatment of CKD is an individualized treatment approach to stop further CKD progression, cardiovascular risk management, appropriate dose modification for the medicines, removal of possible nephrotoxins, treatment of albuminuria, monitoring and managing complications of CKD, good dietary regimen, exercise, and weight reduction. Early diagnosis of CKD and appropriate treatment are crucial in controlling the risk factors responsible for CKD progression thereby reducing CKD mortality and morbidity and associated medical expenditure throughout the world.

Conflicts of Interest

The author has no conflict of interest.

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