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# Chronic Kidney Disease: An Updated Review

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**ABSTRACT**

Chronic Kidney disease (CKD) is recognized as a global public health problem which is increasing rapidly in low and middle income countries. Renal dysfunction may lead to multiple morbidities including hypertension, Diabetes mellitus, Cardiovascular disease, anemia, kidney stones, chronic kidney disease-Mineral and bone disorders (CKD-MBD). This review summarizes what the literature has so far provided from guidelines to diagnosis of CKD and also overlooks into the estimation of renal function. It also presents a general overview about the risk factors of CKD, the morbidities associated with this disease, specifically with its more severe classic form. Finally, the review stresses on the various aspects of treatment both pharmacological and non-pharmacological currently used in the management of this condition.

## INTRODUCTION

In developed and developing countries Chronic Kidney disease (CKD) represents a major public health problem[1]. Chronic renal failure (CRF) or chronic kidney disease (CKD) is an irreversible progressive reduction in kidney function. CKD is defined as sustained kidney damage indicated by the presence of structural or functional abnormalities (e.g.; microalbuminuria/protenuria, hematuria, histologic or imaging abnormalities), and or reduced glomerular filtration rate (GFR) to less than 60ml/min/1.73m$^2$ for at least 3 months[2, 3].

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem[4]. With the fastest growth occurring in low-income and middle-income countries the prevalence and associated burden of CKD is rising worldwide[5-7]. The global prevalence of CKD was estimated at about 10%, corresponding to almost 500 million people, with similar estimates in men and women, and in high-income countries compared with low-income countries[8].

Rapidly occurring urbanization has contributed to the rise of kidney disease and other non-communicable diseases in low and middle income countries[9]. Commonly associated lifestyle changes and rapid urbanization has made people live in settings where a growing prevalence of non-communicable diseases is juxtaposed [10].

Total cost of the treatment of chronic kidney disease which is in milder form appears to be much greater than the total cost of treating end-stage kidney disease globally. In 2015, in the United States of America, for example, more than 64 billion and 34 billion United States dollars respectively were the Medicare expenditures on chronic and end-stage kidney disease[11]. Much of the expenditure, morbidity and mortality previously attributed to diabetes and hypertension are attributable to kidney disease and its complications[12, 13.] Therefore, accurate and early diagnosis of kidney disease is necessary not only to prevent future health co-morbidities but also to reduce financial cost and burden[9].

Since publication of Kidney/Dialysis outcome Quality Initiative (K/DOQI) in the fall of 1997, National Kidney Foundation (NKF) Dialysis outcome Quality Initiative (DOQL) guidelines have become an integrated part of nephrology practice throughout America and many parts of the world including India[14].

This review summarizes the most relevant and recent reports related to CKD, briefly addressing the classification of the disease into different stages, pathophysiology of the

disease, then dwelling in more depth into its diagnostic criteria. Moreover, the discussion includes morbidities associated with CKD and information about the various treatment regimens is provided. Throughout the review, emphasize is laid on the complexity of CKD in terms of stages of CKD, pathophysiology, diagnosis, morbidities, and the treatment approaches.

## ETIOLOGY

The exact pathophysiology of CKD is complex and remains largely unclear. The risk factors include diabetes mellitus, hypertension, glomerulonephritis and acute kidney injury, polycystic kidney disease, family history of kidney disease, age > 55 years, obesity or metabolic syndrome, long-standing vascular disease (e.g., renal artery stenosis), long-standing obstructive uropathy (e.g., renal calculi), exposure to nephrotoxic agents[15,16].

## PATHOPHYSIOLOGY

Angiotensin II, a potent vasoconstrictor of both the afferent and efferent arterioles affects the efferent arterioles, which increases the pressure in glomerular capillaries. Development of intraglomerular HTN correlates with development of systemic arterial HTN resulting in albuminuria and proteinuria. This accelerates the progressive loss of nephrons due to direct cellular damage. Unregulated production of inflammatory and vasoactive cytokines leads to intratubular complement activation followed by damage in the progressive proteinuric nephropathies and scaring of the interstitium. Thus leading to progressive loss of structural nephron units and reduced GFR.[17]

## DIAGNOSTIC CRITERIA FOR CKD

A patient is identified with CKD if abnormalities of kidney structure or function were present for a minimum of 3 months according to the KDIGO CKD guidelines (and the English (NICE) National Institute for Health and Care Excellence CKD guidelines),. The abnormalities are shown in Table 1.

**Table No. 1: Diagnostic criteria for CKD[18].**

| Diagnostic criteria for CKD | |
|---|---|
| For at least 3 months one of the following needs to be present: | |
| 1. | Decreased eGFR (<60 mL/min/1.73 $m^2$). |
| 2. | One or more marker of kidney damage:<br>i. Albuminuria (urinary albumin-to-creatinine ratio [ACR] ≥30 mg/g [3 mg/mmol])<br>ii. Structural abnormalities (from imaging)<br>iii. Urine sediment abnormalities (hematuria, red or white blood cell casts, oval fat bodies or fatty casts, granular casts, and renal tubular epithelial cells)<br>iv. Electrolyte and other abnormalities due to tubular disorders<br>v. Histological abnormalities<br>vi. Previous history of kidney transplantation |

**DIAGNOSIS OF CKD**

In its early stages, CKD usually causes no symptoms. Developing problems can be detected only through lab tests. Diabetes, hypertension and family history of kidney disease are high risk groups. If increased risk for chronic kidney disease is detected in the laboratory tests then the patient should be routinely tested for development of this disease. The tests include the following:

**1. Blood Tests typically show:** Elevated BUN and serum creatinine concentration, reduced arterial pH and bicarbonate concentration, reduced serum calcium level, Increased serum potassium and phosphate levels, Possible reduction in the serum sodium level,normochromic, normocytic anaemia(hematocrit 20% to 30%).

**2. Urinalysis:** The urine is examined for the identification of red and white blood cells, and the presence of solid materials such as stones, casts and crystals or frothing excessively in proteinuria.

**Twenty-four-hour urine tests:** This test requires the collection of urine for 24 consecutive hours. For the presence of protein and waste products (Urea, Nitrogen and Creatinine) the urine may be analyzed. The presence of protein in urine indicates kidney damage.

**Glomerular Filtration Rate (GFR):** The GFR is a standard means of expressing overall kidney function derived from serum creatinine. As kidney disease progresses, GFR falls. About 100-140 ml/min in men and 85-115 ml/min in women is the normal GFR.

**3. Radiographic Findings:** The following radiographic tests may be performed: Kidney, ureter, and bladder radiography, IV pyelography, renal scan, renal arteriography, and nephrotomography typically; these tests reveal small kidneys (less than 8cm in length).

**4. Other Tests:** To evaluate the disturbances in kidney functions, different tests are performed such as: tests for electrolyte and acid-base balance (Sodium, Potassium, Magnesium, and Bicarbonate), tests for Anaemia (hematocrit, ferritin, transferrin saturation, and peripheral smear), tests for bone disease (calcium, phosphorus, alkaline phosphatase, and parathyroid hormone), other general tests (serum albumin, cholesterol, triglycerides, blood glucose and haemoglobin A1C) and ECG and echocardiography[17].

**ESTIMATION OF RENAL FUNCTION**

GFR is the product of mean filtration rate of each sole nephron multiplied by the total number of nephrons present in both kidneys. Normal GFR level is around 130 ml/min/1.73m$^2$ for men and 120ml/min/1.73m$^2$ for women, with significant difference amongst individuals based on age, gender, body mass, diet, physical activity, pharmacological therapy and physiological states e.g. pregnancy[19]. The adult GFR can be computed by applying any of the following equations:

➢ **Cockcroft-Gault (CG) equation:** In 1973, CG equation was developed to predict the creatinine clearance (Ccr) from serum creatinine (Scr), age and body weight. The CG formula is expressed below:

$$C_{cr} = (140 - age) \times weight\ (Kg) / 72 \times S_{cr} [\times 0.85 \text{ if female}]$$

➢ **Modification of Diet in Renal Disease (MDRD) study equation:** The MDRD study equation was developed in 1999 using data including Caucasian and African-American CKD patients with GFR from 5-90 ml/min/1.73m2 body surface area as stated under:

$$\text{MDRD eGFR} = 186 \times (Scr)^{-1.154} \times (age)^{-0.023} [\times 0.742 \text{ if female}] [\times 1.21 \text{ if black}].$$

This equation only requires data of serum creatinine, age and gender[20].

➢ **Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation:** The MDRD study equation was developed in CKD population and its major limitations were imprecision and systematic underestimation of GFR at levels > 60ml/min/1.73m$^2$. Therefore, a more accurate equation named CKD-EPI creatinine equation was designed which is given below:

$$eGFR = 141\times \min(S_{cr}/k, 1)^{\alpha} \times \max(S_{cr}/k, 1)^{-1.209} \times 0.993^{Age} [\times 1.018 \text{ if female}] [\times 1.159 \text{ if black}]$$

Where $S_{cr}$ is Serum creatinine (mg/dl); k is 0.7 for females and 0.9 for males; α is --0.329 for females and -0.411 for males; min is minimum of Scr/k or 1; max is maximum of Scr/k or 1.

➢ **CKD-EPI cystatin C equation:** Serum cystatin C level alone as a replacement for Scr in estimation of renal function provided GFR estimates as accurate as $S_{cr}$. The CKD-EPI cystatin C equation is stated as:

$$eGFR = 133 \times \min (SCysC/0.8, 1)^{-0.499} \times \max (SCysC/0.8, 1)^{-1.328} \times 0.996^{Age} [\times 0.932 \text{ if female}]$$

Where SCysC is Serum cystatin C; min is minimum of SCysC/0.8 or 1; max is maximum of SCysC/0.8 or 1.

➢ **CKD-EPI creatinine-cystatin C equation:** The equation comprising SCys C level in combination with Scr level, sex, age and race provided the supreme accurate GFR estimates. The CKD-EPI creatine-cystatin C equation is given below:

$$eGFR = 135 \times \min(S_{cr}/k, 1)^{\alpha} \times \max(S_{cr}/ k, 1)^{-0.601} \times \min (SCysC / 0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age} [\times 0.969 \text{ if female}] [\times 1.08 \text{ if black}]$$

Whereby $S_{cr}$ is Serum creatinine (mg/dl); SCysC is Serum cystatin C (mg/l); k is 0.7 for females and 0.9 for males; α is -0.248 for females and -0.207 for males; min(Scr/k , 1) is minimum of Scr/k or 1; max(Scr/k, 1) is maximum of Scr/k or 1; min(SCysC/0.8, 1) is minimum of SCysC/0.8 or 1; max(SCysC/0.8, 1) is maximum of SCysC/0.8 or 1.[21]

**SIGNS AND SYMPTOMS**

According to the stage of CKD, signs and symptoms may vary. These may be developed in early stages and worsen prominently in the end stages. They include loss of appetite,

increased or decreased urination, feeling tired, nausea and vomiting, shortness of breath, azotemia, swollen feet/ankles, muscle cramps, sleep problems, chest pain, and skin pigmentation, trouble concentrating, and swelling of face or around the eyes especially in the morning[22].

## RISK FACTORS

To assess the progression of CKD and the stage of renal failure risk factors are used. It includes the following: age, obesity, diabetes mellitus (DM), hypertension, genetic component, family history, socioeconomic status, smoking, gender, nephrotoxins, acute kidney injury, established heart problems, newly defined risk factors[23].

## MORBIDITIES AMONG CKD PATIENTS

Patients with CKD are known to suffer from various co-morbidities and complications as a cause or consequence of renal disease[24]. The common co-morbidities of CKD include:

**Hypertension:** Approximately 80% of CKD patients have hypertension and it is an imperative risk factor not only to renal disease progression towards end-stage renal failure (ESRF) but also to cardiovascular events[26].

**Diabetes mellitus:** The prevalence of DM in CKD population Of 9,536 NHANES participants, (18.3%) were identified with CKD and (11.8%) were identified with diabetes[27].

**Cardiovascular disease:** Cardiovascular disease (CVD) is a major cause of morbidity and mortality among patients with chronic renal disease (CRD). High prevalence of CVD among incident dialysis patients suggests that CVD begins in earlier stages of CRD[28].

**Anemia:** Anemia is a common co-morbidity of chronic kidney disease (CKD). The ability to produce the erythropoietin which is essential for the production of hemoglobin is lost by the diseased kidney. The age-related rise in CKD makes anemia in CKD a problem of increasing prevalence among residents of long-term care facilities[29].

**Kidney stones:** Studies prove that a history of kidney stones is associated with increased risk of CKD[30].

**Chronic kidney disease-Mineral and bone disorders (CKD-MBD):** Disturbances in mineral and bone metabolism are prevalent in chronic kidney disease (CKD) and are an

important cause of morbidity, decreased quality of life, and extraskeletal calcification that have been associated with increased cardiovascular mortality. These disturbances have been classified based on bone biopsy and traditionally been termed renal osteodystrophy[31].

## MANAGEMENT OF CHRONIC KIDNEY DISEASE

The overall goal of therapy in individuals with CKD is to delay or prevent progression of the disease, thereby minimizing the development or severity of associated complications and ultimately limiting the progression ESRD when haemodialysis, peritoneal dialysis or kidney transplantation is required.

### Non-pharmacological therapy

### 1. All patients with CKD are treated initially by medical management (Medicine, Dietary Advice and Monitoring)

**Diet:** Meta- analyses to determine the effect of protein restriction on the progression of CKD suggest only a relatively small benefit from dietary protein restriction. Protein restriction to 0.8g/kg/day is recommended only in patients with eGFR less than 30mL/min/1.73m$^2$ with appropriate monitoring by dietician to avoid malnutrition. High sodium intake can increase blood pressure and proteinuria, blunt the response to renin-angiotensin system (RAS) blockade and include glomerular hyperfiltration; therefore decreasing salt intake to less than 2g or 90mEq per day of sodium is recommended in patients with hypertension or proteinuria.

**Smoking cessation and exercise:** Smoking cessation is encouraged to slow progression of CKD and to reduce the risk of CVD. Clinicians should educate patients regarding the risk and institute appropriate therapeutic options for smoking cessation. People with CKD are encouraged to exercise at least 30 minutes five times per week and achieve a healthy body weight to maintain a BMI of 20 to 25 kg/m$^2$.[32]

### 2. Severe damage in CKD (ESRD) requires kidney replacement by dialysis or transplant.

**Dialysis:** When renal failure or ESRD becomes totally irreversible and condition worsens, it is appropriate to recommend dialysis to filter the body wastes. Dialysis type is to be selected based upon the patient condition, complaints, vascular access or peritoneal access. It lowers the risk of morbidity and mortality, increases the life span from 10 to 15 years.

**Types of dialysis:** There are primary and secondary types: Primary dialysis includes hemodialysis, Peritoneal and hemofiltration, Secondary dialysis includes hemofiltration and intestinal dialysis.

### 3. Renal Transplantation

If patient's renal function is not controlled by dialysis, or if kidney is not responding properly to dialysis and medication and if the condition worsens, then renal transplantation is recommended[17].

## PHARMACOLOGICAL THERAPY

### Diabetes with CKD

Prevention of diabetic complications, particularly CKD, by long-term intensive glycemic control from early in the course of diabetes is well established for DM1 and DM2[34,35].

**Table No. 2: Treatment for Diabetes with CKD[36]**

| **Hypoglycemic Agents: Dosing Requirements In Patients With Chronic Kidney Disease** | | |
|---|---|---|
| **Drug** | **Usual Dosage** | **Special Considerations** |
| 1. Chlorpropamide | 100 to 500 mg daily | Avoid in patients with GFR less than 50 ml /min because of increased risk of hypoglycemia |
| 2. Glipizide | 5 mg daily | No dosage adjustment needed |
| 3. Metformin | 500 mg twice daily | Avoid if serum creatinine level is higher than 1.5 mg /dl in men, higher than 1.4 mg/dl in women and in patients older than 80 years or with CHF; Fixed-dose combination with metformin should be used carefully in renal impairment. Metformin should be temporarily discontinued for 24-48 hours before used of iodinated contrast agents. |

**Hypertension with CKD**

In practice, the treatment of hypertension is often based on BP recordings[37]. These may be inaccurate due to lack of repeat measurements, diurnal variation in BP and whitecoat hypertension[38].

**Table No. 3: Treatment for Hypertension with CKD[39, 40]**

| **Antihypertensive Agents: Dosing Requirements in patients with Chronic Kidney Disease** | | | | |
|---|---|---|---|---|
| **DRUG** | **Usual Dose** | **Dosage adjustment based on GFR (ml/min/1.73 m² )** | | |
| | | **> 50** | **10 to 50** | **< 10** |
| ACE inhibitors<br>1.Enalapril | 5 to 10 mg every 12 hours | 100 % | 75 to 100 % | 50 % |
| 2. Lisinopril | 5 to 10 mg daily | 100 % | 50 to 75 % | 25 to 50 % |
| 3. Ramipril | 5 to 10 mg daily | 100 % | 50 to 75 % | 25 to 50 % |
| Beta Blockers | | | | |
| 1. Atenolol | 5 to 100 mg daily | 100 % | 50 % | 25 % |
| 2. Nadolol | 40 to 80 mg daily | 100 % | 50 % | 25 % |
| Diuretics | | | | |
| 1. Furosemide | No adjustment needed | - | - | - |
| 2. Spironolactone | 50 to 100 mg daily | Every 6 to 12 hours | Every 12 to 24 hours | Avoid |
| 3. Torsemide | No adjustment needed | - | - | - |
| 4. Amiloride | 5 mg daily | 100 % | 50 % | Avoid |

**Hyperlipidemia with CKD**

Lipoprotein abnormalities such as low levels of high-density lipoprotein (HDL) and high triglycerides (TGs), associated with the metabolic syndrome, are also associated with subsequent decline in kidney function[41].

**Table No. 4: Treatment for Hyperlipidemia with CKD[42,43]**

| Statins: Dosing Requirements in Patients with Chronic Kidney Disease | | |
|---|---|---|
| Drug | Usual Dose | Dosage adjustment based on degree of renal function |
| 1. Atorvastatin | 10 mg daily<br>Maximum dose: 80 mg daily | No adjustment needed |
| 2. Lovastatin | 20 to 40 mg daily<br>Maximum dose :<br>80 mg daily (immediate release)<br>60 mg daily (extended release) | Use with caution in patients with a GFR less than 30 ml/min/ 1.73m² |
| 3. Rosuvastatin | 5 to 40 mg daily | Recommended starting dosage is 5 mg daily in patients with GFR less than 30 ml /min/1.73m² not exceed 10 mg daily |

**Other therapies used in CKD**

If the GFR is below 60 mL/min, i.e., if the patient is in CKD stage 3 or higher, certain drugs should no longer be given, either because they tend to damage the kidneys or because they are insufficiently eliminated by poorly functioning kidneys and will therefore accumulate in the body and cause toxic side effects on other organs [44].

**Table No. 5: Other Therapies used in CKD[39, 45]**

| **Antimicrobial Agents: Dosing requirements in Patients with Chronic Kidney Disease** | | | | |
|---|---|---|---|---|
| **Drug** | **Usual Dosage** | **Dosage adjustment based on GFR ( ml/min/1.73 m² )** | | |
| | | **> 50** | **10 to 50** | **< 10** |
| Antifungals<br>1. Ketoconazole | No adjustment needed | - | - | - |
| Carbapenems<br>1. Meropenem | 1 -2 gm every 8 hours | 100 % | 50 % every 12 hours | 50 % every 24 hours |
| Cephalosporin<br>1. Cefixime | 200 mg every 12 hours | 100 % | 75 % | 50 % |
| 2. Cefoperazone | No adjustment needed | - | - | - |
| 3. Cefotaxime | 1 to 2 gm every 6 to 12 hours | Every 6 hours | Every 6 to 12 hours | Every 24 hours or 50 % |
| 4. Ceftriaxone | No adjustment needed | - | - | - |
| 5. Cefuroxime | 0.75 to 1.5 gm every 8 hours | Every 8 hours | Every 8 to 12 hours | Every 12 hours |
| Macrolides<br>1. Azithromycin | No adjustment needed | - | - | - |
| 2. Clarithromycin | 250 to 500 mg every 12 hours | 100 % | 50 to 100 % | 50 % |
| 3. Erythromycin | No adjustment needed | - | - | - |
| Tetracycline<br>1. Doxycycline | No adjustment needed | - | - | - |
| Quinolones<br>1. Ciprofloxacin | 400 mg IV or 500 to 750 mg orally every 12 hours | 100% | 50 to 75% | 50 % |

**Table No. 6: Other Common Agents: Dosing Requirements in CKD[46]**

| Other Common Agents: Dosing Requirements in Patients with Chronic Kidney Disease | | | | |
|---|---|---|---|---|
| **Drug** | **Usual Dosage** | **Dosage adjustment based on GFR ( ml/min/1.73 m² )** | | |
| | | **> 50** | **10 to 50** | **< 10** |
| 1. Metoclopramide | 10 to 15 mg thrice a day | 100 % | 75 % | 50 % |
| 2. Omeprazole | No adjustment needed | - | - | - |
| 3. Ranitidine | 150 to 300mg at bedtime | 75 % | 50 % | 25 % |

**Anemia of chronic kidney disease**

The desired outcome of anaemia management are to increase oxygen carrying capacity, decrease signs and symptoms of anaemia ,improve the patient's quality of life, and decrease the need for blood transfusion. Achievement of these goals requires a combination of an Erythropoietin –Stimulating Agent and iron supplementation to promote and maintain erythropoiesis.

**Table No. 7: Treatment for Anaemia of Chronic Kidney Disease[32]**

| Treatment for Anaemia of CKD | |
|---|---|
| **IV Iron Therapies** | |
| **Iron Replacement** | **Dosing (nondialysis)** |
| 1. Iron Dextran | 100 mg IV or IM daily for 10 doses<br>OR<br>250 to 1000 mg slow IV infusion |
| 2. Iron Sucrose | 200 mg IV x 5 doses in 14 days<br>500 mg slow IV infusion on days 1 and 14<br>300 mg , 400 mg IV infusion all 14 days |
| 3. Sodium Ferric Gluconate | 250 mg slow IV infusion |
| 4. Ferumoxytol | 510 mg IV x 2 doses 3 to 8 days |
| ESA Therapies | |
| Treatment | Dosing (nondialysis) |
| 1. Darbepoetin alfa | Initial : 0.45 mcg /kg IV or SC every 4 weeks |
| 2. Epoetin alfa | Initial: 50 – 100 U/kg IV or SC 3 times a week |

## CONCLUSION

This review summarizes the contents arrived out of the literature survey. Morbidities emphasizes the complexity of this disease as a condition that affects many bodily systems moreover affecting the quality of life. Therefore, the management of this varied entity requires a skilled and knowledgeable multidisciplinary team who can achieve best patient outcomes. It is imperative to remember that the treatment of CKD changes throughout different stages. Early detection of long-term morbidities through appropriate screening tests constitutes an essential part of the management of this condition.

Guidelines strongly recommend lifestyle modifications as a critical part of the management. Based on the different co-morbidities present, the drug treatment of CKD tends to change. The other treatment options like dialysis and renal replacement therapy are helpful in the management of CKD.

In conclusion, we hope this review provided an updated summary that sheds light over the complex nature of CKD. Future research has to focus on the missing blocks in our growing knowledge about the various conditions of the disease which may help providing perfect care to the patients.

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