An overview on Chronic Kidney Disease allied risk factors and complications

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ABSTRACT

Chronic kidney disease is a long term condition characterised by the gradual loss of kidney function at least a period of 3 months or more. About two-third of the cases are mainly caused due to HTN and DM. The symptom load plays a crucial role in the patient's disease experience and among the main signs of CKD are troubling physical and psychological symptoms. The evaluation of the symptom burden of CKD patients is of the utmost importance in clinical management. The risk factors include age, sex, race and ethnicity, family history, drug use, smoking, and socioeconomic status; and other comorbidities, such as hypertension and diabetes. Some risk factors can be modified and prevent or slow down the progression to ESRD. CKD progression is associated with serious complications such as cardiovascular risk, dyslipidemia, anemia, nutritional issues, and mineral and bone disorders.

Keywords: Chronic kidney disease; End-stage renal disease; Risk factors; Complications; Prevalence.

INTRODUCTION

In normal people, the kidneys, weighing about 4 ounces each, filters about 200 litres of blood daily to remove waste products and excess water. Renal metabolizes 25-hydroxyvitamin D to calcitriol, which is an active ingredient, controls calcium absorption from foods taken and facilitates bone formation. They are essential for the development of erythropoietin, which promotes the synthesis of erythrocytes via the bone marrow. A hormone called renin is secreted by juxtaglomerular kidneys, which helps control blood volume and blood pressure. Whilst dialysis can replace some kidney functions, it cannot mimic the normal kidney function's biosynthetic and metabolic activities.[1]

Chronic kidney disease: In 2002, the US NKF KDOQI clinical practice guidelines defined chronic kidney disease as renal failure or glomerular filtration rate lower than 60 mL/min per 1.73 m^2 for a period of 3 months or more, and developed a system to classify based on the estimated glomerular filtration rate.[2]

CKD staging

Evaluation and justification for the measures of CKD severity, and the NKF created standards as a feature of its K/DOQI to stratify CKD patients:

Stage 1: normal eGFR 90 mL/min/1.73 m^2 and constant albuminuria

Stage 2: eGFR 60- 89 mL/min/1.73 m^2

Stage 3: eGFR 30- 59 mL/min/1.73 m^2

Stage 4: eGFR 15 - 29 mL/min/1.73 m^2

Stage 5: eGFR below 15 mL/min/1.73 m2 or end-stage renal disease.[3]

Epidemiology

CKD has developed into a potential risk factor for global morbidity and death. Earlier, in developing countries it was perceived as a major health concern with 4 out of 5 cases of death from chronic kidney disease occurring in low to average income countries. The death rate will rise from 3.78 million in 1990 (40.4% of all deaths) to 7.63 million in 2020 (66.7% of all deaths) in india.[4]

In America around 1 in 9 adults have CKD and a minority suffer from their terminal condition, ESRD.[3, 5]

In America the prevalence of CKD stages is as follows: 1.8 percent of stage 1, 3.2 percent of stage 2, 7.7 percent of third stage, and 0.35 percent of stage 4 and 5. Patients with stage 3 or 4 illnesses can advance to

stage 5 at a rate of 1.5% per annum. Phase 1 or 2 develop into more advanced stages of CKD at around 0.5 percent per year.[6]

Symptoms: Symptom burden plays a central role in the patient's experience of the disease and troublesome physical and psychological symptoms are among the main manifestations of CKD. The typical symptoms are fatigue, pruritus, irritability, anxiety, and nausea. Assessment of the symptom burden of all CKD patients is very essential in clinical management. However, evidence reveals that healthcare professionals frequently under recognize and under-treat the physical symptoms, with patients subsequently experiencing immense physical and physiological trauma.[7]

Risk factors: It is important to identify individual predisposing factors for CKD in terms of personal and community health, since such risk factors can be changed and avoided or the objective is to analyse lifestyle factors such as age, sex, race and ethnicity, family history, medication use, smoking, socioeconomic status; and other co-morbidities such as high blood pressure, high blood glucose levels.[8] are mentioned in (Table 1)

Table 1: Risk Factors

Non Modifiable risk factors	Modifiable risk factors
Family History	Obesity
Gender	Smoking
Age	Nephrotoxins
Race	Hypertension
Ethnicity	Diabetes
Low birth weight	

Family history: CKD patients' family history has an elevated incidence of CKD and its risk factors. Hereditary conditions and urological causes involve almost 23% of patients with incident dialysis who had immediate relatives with ESRD.[9]

Gender: Many registries like the Japanese Society for Dialysis Therapy have illustrated that ESRD is more common among men.[10] In contrast, the CREDIT study demonstrated that CKD is higher in women than in men (18.4 vs. 12.8%) in Turkey.[11]

Ethnicity: Several findings in the US have proved that there is higher risk of developing ESRD in African Americans relative to Caucasians.[12] The risk of hypertensive ESRD is nearly five times higher in African Americans.[13] Recent findings reported that the lifetime risk of developing ESRD was found to be 7.8 percent for 20-year-old black women, 7.3 percent in case of black men, 1.8 percent in case of white women, and 2.5 percent for white men.[8]

Age: Renal function drops dramatcally with age in both men and women. Amongst the elderly population, more than one-half of the subjects diagnosed with CKD stages 3-5 (GFR 60 ml/min per1.73 m2) were recognised by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.10 Thus, the elderly population more likely prone to develop CKD after various renal injuries.[14, 15]

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Low birth weight: In the 1980s, Brenner and his colleagues proposed that restriction of intrauterine growth could lead to low counts of nephrons, which may cause high blood pressure and renal dysfunction (also known as the Barker hypothesis).[16] Nephron count have been appeared to increase by 257.426 glomeruli per kg of birth weight in assistance of this theory.[17] Low counts of nephrons contribute to intraglomerular hypertension and hyperfiltration in the available nephrons and lower over-all GFR and increased albumin-to-creatinine ratio in urine. Reduced birth weight and restrictions on intrauterine growth were positively correlated with higher risk of ESRD among Norwegians.[18]

Obesity: Obesity was among the most modifiable primary factors causing the ESRD in the 21st era. Glomerular hypertrophy and hyperfiltration increase renal injury by increasing the capillary wall tension of the glomeruli and lowering the density of the podocyte.[19] Obesity can lead to pathogenesis of CKD by inflammatory mediators, , prothrombotic condition, hypervolemia, oxidative stress, dysfunction of endothelium, and adipokine derangements.[20] Apart from increased BMI, increased weight round the abdomen was linked with greater risk of CKD.[21]

Socioeconomic status: Socioeconomic status may be determined by income, occupation, education, wealth, and housing situation.[22]

Smoking: Smoking enhances CKD risk through oxidative stress, by endothelial dysfunction, glomerulosclerosis, proinflammatory state, tubular atrophy and prothrombotic shift.[20]

Nephrotoxins: Alcohol and recreational medicinal products were related to CKD development as well as improper use of analgesic medicinal products and exposure to heavy metals.23 Patients consuming less than a thousand paracetamol medicinal products were used for comparison, the odds ratio for ESRD was found to be 2.0., for those who had taken 1000 – 4999 tablets, and 2.4 for those who had taken 5000 or more tablets.[24]

Diabetes Mellitus: Diabetes mellitus (DM) is the primary CKD and ESRD etiology in both developed and still developing countries.[25] Mechanisms contributing to diabetes kidney disease include hyperfiltra-

tion damage, advanced end products for glycosylation, and ROS (reactive oxygen species). At the molecular level, growth factors, various cytokines, hormones such as the growth factor-beta and angiotensin II transformation induce pathological changes related to diabetic nephropathy.[26]

Hypertension: Hypertension has long been a etiology of kidney impairment and constitutes 27% of all patients with ESRD in America and 28% of patients with hemodialysis in Turkey.[27] Systemic hypertension due to intraglomerular capillary tension leading to glomerulosclerosis and loss of kidney function; a transient risk of diminished renal function was documented in hypertensive subjects. Important hypertension is found in age groups of 25 to 45 years, but kidney impairment does not occur unless the subject has minimum 10 years of uncontrolled hypertension.[26] Major risk conditions for CKD include previous experience of, hepatitis C virus, hyperlipidemia, human immunodeficiency virus infection, cardiovascular disease, malignancy and metabolic syndrome.

Newly defined Risk Factors: Obstructive sleep apnea is a condition that has been correlated with total and partial breathing difficulties during sleep for minimum five events per hour. Also proposed as a causal factor for CKD was heart rate. Patients with elevated heart rate are more likely to have lower average GFR and increased risk of developing proteinuria.[28]

Gram-negative tooth-associated bacterial biofilms have also identified periodontal disease as a causal factor for CKD. In such patients the inflammatory response is associated with renal disease.[29]

CKD complications and its management

CKD associated anemia: Anemia is described as a significant reduction in one or more of the main red blood cells measurements hemoglobin levels, packed cell volume, or red blood corpuscle count. Optimal hemoglobin level in men and postmenopausal women is below 13 g/dL, and in premenopausal women below 12 g/d.[30] Normochromic, normocytic anemia generally related to progressive CKD,[31] and thus total prevalence of CKD-related anemia is around 50%. Although anemia are often diagnosed in any stage of CKD patients, the prevalence of anemia and severity of disease are strongly interlinked. One-fourth of patients experiencing from stage 1 CKD; half of CKD patients with stage 2, 3, and 4; and three-quarters of dialysis-initiated CKD patients (stage 5) experience anemia.[32]

Anemia in renally ill-patients may results from many processes (iron, folate, or vitamin B12 insufficiency; gastrointestinal bleeding; significant hyperparathyroidism; systemic inflammation; and decreased red blood cell survivability), reduced erythropoietin formation is more important and specific etiological factor that contributes to anemia in CKD patients. Erythropoietin produced by the interstitial renal fibroblasts[33] is required in the bone marrow for red blood cells to grow and differentiate. In CKD, tubular atrophy tends to cause tubulointerstitial fibrosis, which compromises synthetic ability of renal erythropoietin and results in anemia.

The CKD related anemia is treated by recombinant human erythropoietin (EPO). This technique replaced transfusions as the primary therapy and improved the survival rates in CKD patients with anemia.[34]

CKD associated mineral and bone disorders

The phrase ''CKD associated mineral and bone disorders'' involves defects of bone and mineral metabolism and/or extraskeletal calcification secondary to CKD pathophysiology.[35, 36] The kidney is the primary site for excretion of phosphate and vitamin D1-a-hydroxylation. Patients with renal dysfunction have excessive phosphate levels due to lack of 1, 25 dihydroxy-vitamin D levels indicating decreased parenchymal synthesis. In top of this, renal phosphate excretion is decreased. Simultaneously, these pathways triggers serum calcium levels to decline, leading to increased secretion of parathormone (secondary hyperparathyroidism). The parathyroid hormone has a phosphaturic effect. The parathormone elevates the serum calcium to help bone resorption and promoting 1-a-hydroxylation of 25-hydroxy vitamin D synthesized by the liver which is limited due to reduced kidney reserve from scarring. Increased phosphorus levels are most widely observed in stage 3 CKD patients.[37]

The main aim of CKD-associated bone and mineral disorders therapy is reduction of the phosphorous amount. Initial treatment limits consumption of phosphorus through diet when the levels of phosphate or parathyroid hormone begin to increase. In chronic medical conditions, calcium-based binders are commonly used in the phosphate binders group for CKD-related hyperphosphatemia treatment, and as aluminum-associated toxicity have been documented in aluminum- phosphate binders (aluminium based). While calcium- phosphate binders may induce hypercalcemia, which in particular in the presence of hyperphosphatemia increases the deposition of calcium in the tissue, If indicated (e.g., a patient with CKD with hypercalcemia), use of aluminium - phosphate binders for short period of time remains appropriate; while alternative, calcium-free, phosphates such as the non-absorbable sevelamer have been developed. This has the benefit of losing calcium or aluminum.

Besides phosphate binders, many other groups of drugs have been established to treat the CKD-associated mineral disorder. Given the reduced 1-hydroxylation of vitamin D by the injured kidney, vitamin D and its related compounds could also be needed to boost the serum calcium concentration sufficiently to

Table 2: Statin Dosing in CKD

Statin	Standard dosage (mg/d)	Clearance	Dose range in stages 1-3 CKD	Dose range in stages 4-5 CKD	Use with cyclosporine
Atorvastatin	10-80	Liver	10-80	10-80	Avoid in combination with cyclosporine
Fluvastatin	20-80	Liver	20-80	20-40	Max dose 20 mg/d with cyclosporine
Lovastatin	10-80	Liver	10-80	10-20	Avoid use with cyclosporine
Pitavastatin	1-4	Liver/Kidney	1-2	1-2	Avoid use with cyclosporine
Pravastatin	10-80	Liver/Kidney	10-80	10-20	Maximum dose 20 mg/d when used with cyclosporine
Rosuvastatin	10-40	Liver/Kidney	5-40	5-10	Max dose 5 mg/d with cyclosporine
Simvastatin	5-40	Liver	5-40	5-40	Avoid use with cyclosporine.[48]

suppress parathyroid hormone secretion. CKD patients can also receive calcimimetics that enhance the calcium tolerance of the receptor sensing calcium expressed by the parathyroid gland, decrease the parathyroid hormone secretion and decrease parathyroid gland hyperplasia.

Cardiovascular risk: The cardiovascular risk associated with ESRD has been well established, and the average cardiovascular mortality rate among dialysis patients is 10 to 100 times higher than among age- and sex-factor matched patients in the overall population.[38]

Hypertension is a typical risk factor for the cardiovascular, contributing to cardiovascular risk correlated with CKD. Muntner and his colleagues have shown that hypertension in patients with stage 2-3 CKD are at elevated risk for new or recurrent cardiovascular problems.[39] Systolic blood pressure is more closely associated with cardiovascular mortality in patients with dialysis than pulse or diastolic pressure.[40]

In patients with proteinuric, progressive diabetic and nondiabetic renal disease, angiotensin-converting enzyme inhibitors, or (ARB) angiotensin-receptor blockers, ideal first-line agents with renal protective effects are given.[41]

Inflammation is a less discussed risk factor which is believed to have a significant role in the regulation of CKD related cardiovascular risk. Inflammatory receptors are often elevated in CKD patients, and cardiovascular risk in this population is estimated. Most of the research work in CKD patients have documented that C-reactive protein levels in blood predict cardiovascular outcomes.[42] Proteinuria, a hallmark of renal dysfunction, is associated with elevated cardiovascular disease risk and early cardiovascular mortality in patients with and without diabetes and hypertension.[43, 44]

Dyslipidemia: CKD is strongly linked with dyslipidemia which consists of elevated triglycerides and less HDL-cholesterol. LDL-cholesterol levels (and, thus, overall cholesterol) are not usually increased. CKD leads to lower lipoprotein lipase and LDL receptor control, and increased triglycerides in CKD are caused by delayed catabolism of lipoproteins rich in triglycerides, with no developmental variations.[45] CKD is positively correlated reduced levels of apoA-I (due to reduced hepatic activity) and elevated apoB / apoA-I.46 Reduced activity of lecithin-cholesterol acyltransferase and elevated protein transfer cholesterol esterol (CETP) event lead to reduced levels of HDL cholesterol.[47] Statins are the frequently used lipid-lowering drugs are listed in (Table 2).

Nutritional Issues: When patients progress along the stages of CKD, dietary needs are altered and protein, phosphorus, sodium, potassium, water and metabolism are impaired.

Any modifications in nutrient use contributes to "uremic malnutrition," a syndrome distinct from malnutrition caused by inadequate intake of nutrients. Evaluation of nutritional condition in patients with CKD is critical in resolving the nutritional necessity. Several nutritional markers can be used to evaluate nutritional status. Serum albumin, marker used in all patient populations, due to its simple availability and close association with hospitalization and cause of death.[50]

Lower levels of serum albumin are the most common markers of inadequate clinical results at all stages of CKD, and serum albumin is thus considered a reliable marker of general clinical status.[51] Clinical guidelines recommend maintaining a value of 4.0 g / dL or greater for serum albumin in patients with stage 5 CKD.[52] Serum prealbumin is a sensitive marker for assessing the changes in visceral protein stores with a small body pool and fairly fast turnover of 2-3 days. Levels below 30 mg/dL indicate protein depletion.[53] Low concentrations of serum creatinine are associated with poor clinical results when treating stage 5 CKD. The concentration of serum cholesterol is an independent indicator of mortality in chronic dialysis

patients, and lower serum cholesterol levels can indicate low dietary and energy intake. Serum cholesterol below 150 mg / dL also needs vigilant nutritional status assessment.[54]

A dietary protein intake of less than 0.75 g / kg / d is an early warning signal in patients with low protein and energy intake (as recorded in patients on uncontrolled diets) for acquiring uremic malnutrition. For CKD patients, poor nutrition may warrant initiation of haemodialysis or be an indication for transplant. Nutrient markers such as transferrin, transthyretin, insulin growth factor-1 are reduced and a drop in lean body weight. Other markers implying the necessity for early haemodialysis initiation in ESRD patients involves energy consumption less than 20 kcal / kg / d, and concentration of serum albumin below 4.0 g / dL. Enteral nutrition includes oral proteins, amino acids and/or energy supplements; enteral delivery of nutrients is performed by feeding through nasogastric tubes or percutaneous endoscopic gastroscopy or jejunostomy tubes or through intradialytic parental nutrition. [55]

CONCLUSION

Patients with CKD have many complex management problems to health care providers. The staging system introduced in 2002 by the National Kidney Foundation is a notable accomplishment, which classifies patients according to disease severity. Knowing the predisposing factors and screening of target populations will help to identify and facilitate early management of modifiable risk factors for patients with ESRD. Development of CKD is associated with several complications such as anemia, dietary problems, dyslipidemia, cardiovascular diseases, mineral and bone disorders. Early detection and management by health providers helps in making significant strides toward improving the health of patients with chronic renal disease.

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