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ROLE OF PHARMACIST IN MANAGEMENT OF CHRONIC KIDNEY DISEASE

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ABSTRACT
Chronic kidney disease shows worldwide health events epidemically. s part of a multidisciplinary patient care strategy, clinical pharmacy services have led to improvements in patient care. Pharmacists play an important role in the renal MDT by minimizing drug-related problems, optimizing therapy, laboratory monitoring, determining drug dosage adjustments, developing monitoring plans, avoiding nephrotoxic drugs, managing complications of kidney disease, patient education, and establishing effective medication management programs. Pharmacists represent an essential component of the team through their medication expertise in pharmacotherapy, helping to manage comorbid conditions, slow kidney disease progression, and provide a positive impact on improving the care of kidney patients.

KEYWORDS: CHRONIC kidney disease, Renal function, Pharmacist management.

INTRODUCTION
Chronic kidney disease (CKD) is a progressive disease of declining kidney functions where the nephrons of the kidney are damaged and/or stop functioning and this process is spread over a long period, maybe several months to years. In CKD, the reduction in kidney function is irreversible with a progressive decrease in the glomerular filtration rate, which eventually ends in end-stage renal disease (ESRD). Renal replacement therapies (RRTs) like haemodialysis (making use of an artificial kidney), peritoneal dialysis (using the peritoneal membrane to remove accumulated waste from blood), and renal transplantation are the means of survival once ESRD sets in.[1] It is estimated that 750 million persons across the globe are affected by kidney disease making it a global public health problem.[2] The burden of kidney disease and its detection and management differs worldwide based on socio-economic setting and is influenced by local cultural and political factors.[2] Though several countries have established national data collecting systems like registries for CKD & ESRD, there are inconsistencies in collected data particularly from low- and middleincome countries. High quality data with respect to patients with CKD and not on any mode of renal replacement therapy is limited.[2] World Health Organization‟s (WHO) Global burden of disease 2015 study estimates that reduced glomerular filtration rates directly contributed to over a million deaths, and close to twenty million disability-adjusted life-years (DALYs) and loss of life years of about 18 million from cardiovascular diseases.[3]

The growing number of people with CKD, the number of people progressing to end stage, and the resulting financial load of managing the disease in both first world as well as emergent nations has thrown light upon preventing the occurrence of CKD and minimizing the risk factors. According to a National Health and Nutrition Examination Survey (NHANES) report, in the United States, overall prevalence of CKD (stages 1- 5) gradually increased from 14.2% (2001-2004) to 14.8% (2013-2016) and CKD stage 3 is most prevalent.[4] In Europe, CKD prevalence varied from 4.1% reported in a Swiss study (Swiss Bus Santé study) to 25.5% in a German study (the Northeast German SHIP study) (5). Quality of data from Africa being poor, exact estimates are not reported. A systematic review from Africa reported CKD prevalence from 2-42% from the community-level studies, 11-90% in patients with diabetes, and 13-51% in patients with hypertension (6). A Saudi Arabian study reports 6.5% prevalence of renal insufficiency, 5.4% of diabetic nephropathy, and 1.4% of chronic kidney disease patients among hospitalized inpatients.[7]

In India, a population-based survey has reported an incidence of 151 per million population in Central India,[8] reduced GFR was found in 13% of population,[9] other studies report between 0.8% to 4.8% of reduced

GFR (10,11). According to an Indian CKD registry report published in 2012, among approximately fifty-two thousand registered CKD patients, 48% had ESRD, 16% had CKD of undetermined etiology, hypertensive nephrosclerosis and glomerulonephritis were causes of CKD in 13% and 14% of CKD patients respectively, and the most common cause was diabetic nephropathy (31% of patients).[12] A 5 year follow-up epidemiological study observed that kidney disease patients progressed to ESRD at yearly rates of 23% for those with polycystic kidney disease, 10% for those with glomerulonephritis and 12% for those with diabetic nephropathy, but the risk of death before ESRD was 2-fold higher among diabetic nephropathy patients than those with cystic kidney disease.[13]

CKD is a complex disease with multiple comorbidities and attendant complications. Evidence has accumulated over the years and we now know that the disease is associated with significant morbidity and mortality risks. What makes the disease deadlier is that the metabolic complications associated with it that include mineral and electrolyte imbalance, metabolic acidosis, anemia, and renal osteodystrophy among others may remain asymptomatic for a long time. It is proven now that these complications can significantly affect the physical, and emotional health of a person. A list of other complications of CKD include, cardiovascular disease, secondary hyperparathyroidism, bone and mineral metabolism disorder, uremia and bleeding complications, gout secondary to accumulation of uric acid, and malnutrition due to poor appetite associated with uremia.[14] So, the management of CKD does not involve only controlling the progression of disease and treat underlying disorder but also provide therapy for controlling complications of the disease. Treatment in CKD consists of medications to treat the symptoms of the disease as well as counteract the accumulation of various metabolic wastes as well as mineral and electrolyte disturbances.

Etiology and Pathophysiology of CKD

(I) Risk Factors of CKD

Risk factors for CKD are classified into three categories.

Susceptibility factors, which are associated with an increased risk of developing CKD, but are not directly proven to cause CKD. These factors are generally not modifiable by pharmacologic therapy or lifestyle modifications.[15]

Initiation factors, which directly cause CKD. These factors are modifiable by pharmacologic therapy.

Progression factors, which result in a faster decline in kidney function and cause worsening of CKD. These factors may also be modified by pharmacologic therapy or lifestyle modifications to slow the progression of CKD.[16]

Susceptibility factors

- Advanced age
- Reduced kidney mass
- Low birth weight
- Racial/ethnic minority
- Family history of kidney disease
- Low income or education
- Systemic inflammation
- Dyslipidemia

Initiation factors

- Diabetes mellitus
- Hypertension
- Autoimmune disease
- Polycystic kidney disease
- Drug toxicity
- Urinary tract abnormalities (Infections, Obstruction, Stones)

Progression factors

- Hyperglycemia: Poor blood glucose control (in patients with diabetes)
- Hypertension: Elevated blood pressure
- Proteinuria
- Tobacco smoking

Pathophysiology of CKD

A number of factors can cause initial damage to the kidney. The resulting sequelae, triggers progression of CKD and results in irreversible damage leading to ESKD. The initial damage to kidney may be caused due to any of the initiating factors mentioned above. Whatever the cause, the damage to kidney causes a decrease in the number of functioning nephrons. The remaining nephrons are pressurised to perform kidney functions of filtration and secretion to compensate for the loss of the few nephrons. Initially the remaining nephrons overwork and are able to maintain normal kidney function including serum creatinine and electrolyte levels. With the passage of time, angiotensin II levels are increased. Angiotensin II is a potent vasoconstrictor and under its influence the efferent arterioles are constricted, leading to increased pressure in glomerular capillaries. This may expand the pores of the glomerular basement membrane and allow proteins that are not normally filtered at the glomerulus (due to their high molecular weight) to pass through. The proteins which are not a normal constituent of the filtrate are reabsorbed in the tubules, which can activate tubular cells to release vasoactive cytokines and trigger complement activation. These inflammatory mediators can cause interstitial damage and scarring in the tubules leading to damage that can also affect the reabsorptive function of the kidney. Ultimately, the process leads to progressive loss of nephrons to the point where the number of remaining functioning nephrons is too small to maintain clinical stability, and kidney function declines.[17]

Signs and Symptoms of CKD

Stages 1 and 2 CKD are generally asymptomatic. Stages 3 & 4 may be associated with minimal symptoms. Stage 5 CKD can be associated with severe nausea, and vomiting, muscle pain, breathlessness, fatigue, pruritis and bleeding complications. Most often acute kidney injury also presents with elevations in serum creatinine and severe vomiting. It is important to distinguish between them by taking a careful medical and medication history. In addition to the above symptoms, CKD due to glomerulopathies may present as proteinuria or haematuria. Irrespective of the cause, eventually hypertension is present in all CKD patients in the later stages due to activation of the renin-angiotensin system in the face of failing filtration function of the kidney. Oedema or swelling could be noticed especially in the feet, lower legs, and sometimes the face and hands. This is a sign of a build-up in fluid that can be due to failure of kidneys to excrete sodium and water and also may often be the first sign of protein leakage from the kidneys.[18]

Patients who have advanced kidney disease may exhibit some or all of the following symptoms: loss of appetite, nausea/vomiting, fatigue, tiredness, itching, twitching and a metallic taste in the mouth.[19] These symptoms often indicate that the person is accumulating dangerous amounts of waste products. Patients who display these symptoms are usually at CKD stage 4-5 and often in need of dialysis. (V).

Diagnosis of CKD

The assessment for CKD should include measurement of serum creatinine, urinalysis, blood pressure, serum electrolytes, and/or imaging studies. The primary marker of structural kidney damage is proteinuria, even in patients with normal GFR. Clinically significant proteinuria is defined as urinary protein excretion greater than 300 mg/day or greater than 20 mcg/min in a timed urine collection. Significant proteinuria can also be determined by a spot urine dipstick greater than 30 mg/dL or a urine protein/creatinine ratio greater than 200 mg/g. The NKF recommends routine assessment of proteinuria to detect CKD.

The blood urea nitrogen (BUN) and serum creatinine (SCr) levels may be increased; and GFR decreased in all stages of CKD

Complications of CKD

Impaired Sodium and Water homeostasis

Reduction in the number of functioning nephrons decrease glomerular filtration followed by reabsorption of sodium and water leading to edema. In the normal kidneys, urine osmolality ranges from 50-1200 milliOsmols/L that allows maintenance of water balance with wide range of fluid intake. Similarly, fractional excretion of sodium (FeNa) is 1-3% and allows sodium balance with intake of 120-150meq of sodium per day. In the failing kidneys, as the number of functioning nephrons decreases, the remaining nephrons increase sodium excretion and FeNa may increase up to 10% to 20%.[20]

Impaired potassium homeostasis

Hyperkalemia is estimated to affect more than 50% of patients with stage 5 CKD (66). The fractional excretion of potassium (FeK) is approximately 25% with normal kidney function (67). The GI tract excretes the remaining 5% to 10% of dietary potassium intake. As the number of functioning nephrons decreases, both the distal tubular secretion and GI excretion are increased in the functioning nephrons because of aldosterone stimulation. Functioning nephrons increase FeK up to 100% and GI excretion increases as much as 30% to 70% in CKD, as a result of aldosterone secretion in response to increased potassium levels.

Anemia of CKD[21]

Healthy kidney is responsible for production of 90% of hormone erythropoietin (EPO), which stimulates red blood cell (RBC) production.

Secondary hyperparathyroidism

As kidney function declines in patients with CKD, decreased phosphorus excretion disrupts the balance of calcium and phosphorus homeostasis. Decreased vitamin D activation in the kidney also decreases calcium absorption from the GI tract. The parathyroid glands release PTH in response to decreased serum calcium and increased serum phosphorus levels.

Metabolic acidosis

Approximately 80% of patients with a GFR less than 20 to 30 mL/min/1.73 m2 develop metabolic acidosis.55 Metabolic acidosis can increase protein catabolism and decrease albumin synthesis, which promote muscle wasting, and alter bone metabolism. Other consequences associated with metabolic acidosis in CKD include worsening cardiac disease, impaired glucose tolerance, altered growth hormone and thyroid function, and inflammation.

Renal replacement therapies

Patients who progress to ESRD require renal replacement therapy. The RRT modalities available are dialysis that includes haemodialysis (HD) and peritoneal dialysis (PD), and kidney transplantation. Dialysis should be initiated in stage 4 CKD when GFR falls to below 30ml/min

(I) Haemodialysis

Hemodialysis (HD) involves the exposure of blood to a semipermeable membrane (dialyzer) against which a physiologic solution (dialysate) is flowing. The dialyzer contains many capillary fibres that act like a semipermeable membrane to increase surface area of blood exposure to maximize removal of toxic substances. diffusion – movement of solutes from a region of higher concentration to a region of lower concentration.

(i) Vascular access

Long-term permanent access to perform dialysis is required for haemodialysis. Three primary techniques to obtain vascular access is arteriovenous fistulas (AVF), arteriovenous grafts (AVG), which are permanent and double-lumen venous catheters in the jugular, femoral, or sub-clavian vein that are used as temporary access. An AVF is made by creating an anastomosis between an artery and vein usually in the forearm. An AVG may also be done at a similar site but it uses a polytetrafluoroethylene synthetic graft to connect artery and vein. Though, AVGs are able to be used in 2-3 weeks of grafting when compared to 2-3 months with AVFs, AVF is the preferred access method as it has the longest survival rate and fewest complications. Temporary catheters (double-lumen venous catheters) as mentioned above are used for temporary access while waiting for the AVF or AVG to mature.[22]

(II) Peritoneal Dialysis

The principle of peritoneal dialysis (PD) is similar to haemodialysis where blood is exposed to semipermeable membrane against which a physiologic solution is placed. In PD, the semipermeable membrane is the peritoneal membrane and a sterile dialysate is instilled in the peritoneal cavity. Peritoneal membrane comprises of mesothelial cells that are covered by microvilli and provide increased surface area to the membrane. Blood vessels that supply the abdominal organs, muscle, and mesentery serve as the blood component of the system. Gaps between the mesothelial cells allow for large solutes to pass through into the bloodstream through diffusion. Dialysate instilled into peritoneal cavity for specified length of time to adequately clear metabolic waste products and excess fluids and electrolytes. At the end of the time the dialysate is drained. PD allows for a more physiological removal of solutes and mimics endogenous kidney function. Continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) are types of PD among others.[23]

(III) Kidney transplantation

All patients with ESRD should be considered for renal transplantation if they are healthy enough to undergo transplant surgery. Transplantation is more effective than dialysis from a medical and economical perspective. Kidney transplant procedure is heterotopic, i.e the kidney is implanted above the pelvic bone and ‟ exceptions renal cell carcinoma and polycystic kidney disease). The ureter of trans ‟ T T ‟ T z the antigens displayed by the transplanted organ (alloantigens) that may initiate an immune response against the graft organ. The rejection reaction may be acutewhereby activated T cells infiltrate the graft and trigger immune response or hyperacute – where an immediate immune response against the allograft is initiated due to presence of preformed ‟ antigens (HLA) (common factors like previous organ transplant, multiple blood transfusions, mothers receiving kidney from their children). Chronic rejection reactions involves a slower, insidious affair and is thought to involve both cellmediated (T cells) and humoral-mediated (antibody-mediated rejection reaction) immune processes as well as drug toxicity.[24]

Pharmacist Interventions in Management of CKD

(i) Pharmacist Interventions in healthcare Studies have shown that 50-80% of drug related problems could be prevented. An acceptance rate of 41-96% by prescribers, for interventions suggested by clinical pharmacists to solve or prevent drug-related problems has been reported. Original articles on the effects of pharmacist interventions on different clinical outcomes like interventions on adherence, indicators of drug use, disease-specific and diseasemanagement endpoints describe the positive effects of such interventions.

Most commonly, diuretics that remove excess water from body, phosphate binders to prevent excess absorption of phosphorous from the gut, bone medications like calcium and vitamin D, antihypertensive medications to control hypertension caused by excessive secretion of renal hormones (to maintain adequate blood supply to kidneys), statins to combat cardiovascular risk, medications to lower potassium blood levels, and medications to treat anemia are commonly prescribed.[25] It is common for patients to be admitted to emergency with serious uremic symptoms that requires immediate and urgent haemodialysis using a temporary vascular access to make the patient stable.

The Kidney Disease: Improving Global Outcomes (KDIGO), and National Kidney Foundation (NKF) - Kidney Disease Outcomes Quality Initiative (K/DOQI) has provided guidelines that are revised from time to time and is most referred website. Most guidelines provide recommendations or suggestions of varying strength based on accumulated evidence regarding the identification, detection, prevention of progression and management strategies for chronic kidney disease and/or sustenance therapies for ESRD.

The treatment for disease control in patients with kidney disease is multi-dimensional and inconsistent with multiple prescribed medications, medication adherence issues, and periodic dose adjustments.[16] This may lead to drug related problems in practice and may necessitate repeated monitoring and assessment to ensure goals of therapy, improved medication compliance, and management of risk factors and comorbidities. As CKD progresses from early to later stages, related complications with allied symptoms manifest. Patients with complications are prescribed a mean of 10-12 medications thus making them vulnerable to drug related problems and leading to adherence issues with their regimens.[26]

A study from India reported overdose (19.3%) and ADRs (19.1%) as common DRPs occurring among CKD patients. According to a review, several studies report

poor quality in treatment and management of CKD patients regarding assessment and control of comorbidities, nephrologist referrals, and anticipation of and provision for RRTs. Drug related problems (DRPs) are errors or events due to a drug that occurs during prescribing, dispensing or administering the drug and may include adverse consequences to the drug as well.

To be precise, A drug therapy problem is any undesirable event experienced by a patient that involves, or is suspected to involve, drug therapy and that interferes with achieving the desired goals of therapy and requires professional judgement to resolve.[27] These problems are seen among hospital confined patients and can affect patient morbidity and mortality depending on the severity of the drug related problem. Identifying DRPs and addressing them is as equally important as treating the clinical problems. For many years, pharmacists are known to process pills and sell them. Hepler and Strand introduced the concept of pharmaceutical care in 1990 and gave pharmacists an opportunity to participate in the care of patients directly.[28] Since then pharmacists have provided various clinical pharmacy services like drug therapy review, pharmacist interventions, patient counselling, providing medicine information, detecting and monitoring adverse drug reactions, and medication reconciliations among others. Studies have demonstrated that pharmacist‟s involvement in drug therapy selection and monitoring has improved therapeutic outcomes and minimized drug related problems in patients and reduced treatment costs.[29]

A pharmacists‟ primary responsibility is to provide pharmaceutical care that is defined as “the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient‟s quality of life” (ASHP Statement on pharmaceutical care). Though the concept of pharmacists participating in patient care directly was initially introduced in the United States, other countries caught on and the practice spread across the globe. The need for practicing Clinical Pharmacists was also abetted by rising prevalence of chronic lifestyle diseases as well as severe infectious diseases that called for increased, more efficient and costeffective healthcare. Those patients with chronic diseases and multiple comorbidities usually receive complex treatment regimens that require monitoring of therapy for safety and effectiveness and also are candidates for education on disease as well as medications wherever required to ensure drug therapy effectiveness. By being an integral member of the healthcare team, a pharmacist can help in relieving the workload of physician/general practitioner, increase the efficiency of the healthcare team as well as help healthcare professionals to stay updated on best practices. They can also increase the quality of care in general by interacting directly with patients to improve their adherence to medications, and manage safety and drug interaction issues.[30]

Drug therapy monitoring is a continuous process where a pharmacist reviews patient records and identifies any drug related issues that include drug therapy problems and adverse drug events. The identified issues are communicated to the prescribers along with suggestions or recommendations to solve the problem with the aim of resolving them.

Since clinical pharmacists are increasingly involved in detecting and managing drug-related problems, a convenient tool to aid them in documenting their daily activities is desirable. Most studies have described pharmacist interventions in relation to the drug related problem identified. For eg. For DRP „untreated indication‟ – intervention would be drug therapy started or new drug added; for over dosing or under dosing the intervention would be dosage adjustment/dose adaptation. In practice, few tools are available that are meant specifically for classifying pharmacist interventions. Most hospitals and/or pharmacist working groups have developed their own documentation forms or tools for recording pharmacist interventions. A classification for interventions called The Pharmaceutical Care Network Europe Foundation (PCNE) classification[30] has been developed for use in research to characterize the nature, incidence, and prevalence of DRPs as well as a measurement yardstick in studies that assess outcomes of pharmaceutical care. The classification system is validated and adapted regularly a consequence of which is that several versions of the classification are available for use by the researcher.[31]

In the past few decades, increasing importance is given to the quality of life of patients living with chronic diseases. WHO defines quality of life (QoL) as a recognition of a persons‟ placement in life that is concerned with their culture, moral beliefs and society in which they live in in relation to their purpose, suppositions, and concerns (31). More specifically, researchers assess Health Related Quality of Life (HRQoL) in a patient afflicted with chronic disease, which is a measure of the functional status of an individual in relation to what he/she believes to be ideal. HRQoL is a multidimensional measure and consists of at least three wide areas that include physical, psychological, and social aspects as applies to an individual. Several tools to measure QoL and HRQoL are available to assist researchers in their field of study. There are generic versions of the tools that measure the quality of life for patients with any chronic disease; specific tools to measure quality of life of a patient with specified disease viz. cancer, rheumatoid arthritis, diabetes mellitus, chronic kidney disease etc also exist. The Kidney Disease Quality of Life (KDQoL) is a questionnaire that is intended to measure health related outcomes in patients with chronic kidney disease.[32]

Over the years, healthcare research has focused on economic benefits of healthcare activity in addition to the clinical impact on patient outcomes. Developed

countries have allocated a percentage of their total health budget towards managing chronic kidney disease.

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