EXPLORING THE PERSPECTIVES ON THE MANAGEMENT AND EVALUATION OF THE IMPACT OF CLINICAL PHARMACIST INTERVENTION ON DRUG THERAPY PROBLEMS IN AMBULATORY PATIENTS WITH CHRONIC KIDNEY DISEASE: A MIXED-METHOD APPROACH

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by

KHURSHID ALAM

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DEDICATION

To

my parents…

my wife…

my children: Ayesha, Haniya, Safyyah, Muhammad Zayed, & Muhammad Saad Haris …

For their unwavering affection, motivation, patience, enduring support, and dedication demonstrated throughout the course of my study.

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My guidance depends totally on almighty ALLAH SWT; I have put my trust in Him. To Him I have totally submitted. (11:88)

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reactions
AKI	Acute Kidney Injury (AKI)
ADA	American Diabetes Association
ATC	Anatomical Therapeutic Chemical
AA	Aristolochic Acid
ARF	Acute Renal Failure
AACE	American Association of Clinical Endocrinologists
ACEI	Angiotensin-Converting Enzyme Inhibitors
ARB	Angiotensin II Receptor Blockers
ADME	Absorption, Distribution, Metabolism, And Excretion
BNF	British National Formulary
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CMP	Comprehensive Metabolic Panels
CVD	Cardiovascular Disease
CRI	Chronic Renal Insufficiency
CDC	Centers for Disease Control and Prevent
CVD	Cardiovascular Disease
CN	Consultant Nephrologists
DRP	Drug Related Problem
DM	Diabetes Mellitus
DI	Drug Interactions
DDI	Drug-Drug Interactions
DP	Diastolic blood pressure

DWI	Drug without indication
DIC	Disseminated Intravascular Coagulation
eGFR	Estimated Glomerulus Filtration Rate
EPO	Erythropoietin
ESRD	End Stage Renal Disease
FRD	Failure to receive drug
GP	General Practitioners
Hb	Haemoglobin
HbA1c	Glycated Haemoglobin
IDS	Improper drug selection
HTN	Hypertension
HCP	Healthcare Professionals
IV	Intravenous iron
KDIGO	Kidney Disease: Improving Global Outcomes
LMIC	Low- and Middle-Income Countries
LFT	Liver Function Tests
MRP	Medication-Related Problems
MRN	Medical Record Numbers
MDRD	Modification of Diet in Renal Disease
NCD	Non-communicable Diseases
NHANES	According to the National Health and Nutrition Examination Survey
OTC	Over-The-Counter
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OD	Overdose
PKD	Polycystic Kidney Disease
PCP	Primary care practitioners
PGNR	Postgraduate Senior Nephrology Residents

PPI	proton pump inhibitors
RAAS	Renin-Angiotensin-Aldosterone System
RFT	Renal Function Tests
SBP	Systolic blood pressure
STD	Sub-therapeutic dosage
SPSS	Statistical Package for Social Sciences
SCr	Serum creatinine
SSRI.	Serotonin-Selective Reuptake Inhibitors
SSTI	Soft tissue infections
TM	Traditional Medicines
TDM	Therapeutic Drug Monitoring
PKR	Pakistani Rupees
UI	Untreated Indication
UTI	Urinary Tract Infection
WHO	World Health Organization

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PENEROKAAN PERSPEKTIF PENGURUSAN DAN PENILAIAN KESAN INTERVENSI KLINIKAL TERHADAP TERAPI UBAT DALAM KALANGAN PESAKIT AMBULATORI DENGAN PENYAKIT BUAH PINGGANG KRONIK: SATU PENDEKATAN KAEDAH CAMPURAN

ABSTRAK

Penyakit ginjal kronik (CKD) merupakan sejenis penyakit yang melibatkan kehilangan fungsi ginjal yang biasanya adalah perlahan dan progresif. Penyakit ginjal kronik adalah masalah kesihatan global yang meluas, namun wujud jurang yang ketara dalam memahami faktor-faktor yang membentuk keutamaan rawatan mengikut perspektif pesakit dan penjaga. Tujuan kajian ini adalah untuk menjalankan kajian kualitatif baru untuk meneroka secara perspektif dan pengalaman pesakit dan~~,~~ pakar nefrologi yang berkaitan dengan kaedah pengurusan pesakit dengan CKD dan untuk menilai kelaziman masalah berkaitan ubat (DRP) dan impak kehadiran ahli farmasi klinikal dalam menyelesaikan masalah yang berkaitan DRP dalam pesakit ambulatori. Pendekatan kajian ini merupakan kaedah campuran kualitatif dan kuantitatif. Seramai 11 pakar nefrologi dan 19 pesakit CKD telah dipilih untuk menjalankan kajian kualitatif. Pendekatan fenomenologi deskriptif telah digunakan, yang melibatkan temu bual separa berstruktur secara bersemuka untuk meneroka perspektif dan pengalaman langsung pakar nefrologi dan pesakit yang didiagnosis dengan CKD. Dalam fasa kuantitatif, reka bentuk kajian, secara sebelah pihak serta pra dan pasca intervensi digunakan. Dalam fasa ini, populasi kajian terdiri daripada pesakit dewasa yang disahkan menghidap CKD peringkat 1 hingga 5 dan menjalani rawatan dan susulan di Hospital Pengajaran Khyber (KTH) dan Institusi Pengajaran Perubatan (DHQ),

Bannu. Kesemua pesakit telah diambil dalam tempoh kajian dari Februari 2022 hingga Jun 2022, dan kemudian dari Mac 2022 hingga Julai 2022. Analisis data statistik dilakukan menggunakan program perisian Statistical Package for SocialSciences (SPSS) versi 26 untuk Windows (SPSS, 2019). Nilai p dari dua sisi <0.05 dianggap signifikan secara statistik. Meneroka perspektif pakar nefrologi berhubung populasi yang terjejas CKD di Pakistan, didapati bahawa majoriti penghidap CKD berumur di antara 40 dan 60 tahun dan pesakit yang mempunyai status sosioekonomi yang rendah berkemungkinan besar terdedah kepada CKD. Pakar nefrologi secara konsisten menyatakan bahawa diabetes, hipertensi, dan glomerulonefritis adalah punca utama dan faktor risiko yang berpotensi untuk CKD. Rujukan rawatan yang tertunda dalam kalangan pesakit dengan CKD telah dibuktikan sebagai antara halangan utama, kekurangan perkhidmatan pemeriksaan yang boleh diakses, dan kerumitan melaksanakan pendekatan penjagaan pelbagai disiplin untuk pesakit CKD. Pesakit CKD memberikan perspektif mereka dan menyatakan bahawa buta huruf menghalang mereka daripada membaca dan memahami label preskripsi ubat mereka. Pesakit CKD menyatakan bahawa mereka mengalami gangguan dan kemelesetan ekonomi yang ketara dalam kehidupan harian mereka akibat dari kehilangan punca pendapatan ketidakupayaan untuk bekerja, perniagaan yang terjejas, serta kesukaran mendapatkan ubat ubatan hasilan dari punca pendapatan yang lemah. Secara keseluruhan, halangan yang dihadapi oleh pakar nefrologi dan pesakit adalah saling berkaitan dalam konteks rawatan untuk CKD. Penemuan kajian ini menunjukkan prevalens DRP yang tinggi, dengan setiap pesakit mengalami sekurang-kurangnya satu masalah berkaitan dengan ubat. Purata bilangan masalah berkaitan ubat (DRP) bagi setiap pesakit ditentukan ialah 2.903 dengan sisihan piawai ± 1.148. Jenis DRPs yang paling ketara ditemukan ialah interaksi ubat 167 (45.1%) yang dikurangkan kepada 76 (20.5%) selepas ahli

farmasi campur tangan dan secara statistik didapati signifikan (P= 0.032). Satu lagi jenis DRP yang biasa didapati adalah isu pematuhan yang lemah dalam fasa pra-intervensi (n = 144 (38.9%) dan dikurangkan kepada 80 (21.6%) pada pasca intervensi dan diperhatikan secara statistik (P = 0.042). didapati dalam 137 kes (37.0%). Setelah intervensi yang dilakukan oleh ahli farmasi keadaan ini telah berkurangan dengan ketara kepada 27 kes (7.3%) (P = 0.004). Keputusan regresi logistik berbilang pembolehubah menunjukkan bahawa pesakit dengan CKD peringkat 3, eGFR (G3a 45 - 59 ml/min), adalah 8.838 (95% CI: 2.211 - 35.326) kali lebih berkemungkinan mendapat preskripsi ubat yang salah berbanding mereka. dengan eGFR peringkat 1 (eGFR > 90 ml/min), dengan perkaitan yang ketara (P = 0.002), Begitu juga, pesakit yang diberi 7 hingga 8 ubat berbeza menunjukkan perkaitan yang ketara (P = 0.002) dengan berlakunya DRP,(full stop here) Ini menunjukkan kemungkinan nisbah yang 14.272 kali lebih tinggi risiko (95% CI: 2.650 - 76.871) jika dibandingkan dengan individu yang mengambil 1 hingga 2 ubat. Halangan utama seperti rujukan tertangguh, kekurangan perkhidmatan pemeriksaan yang boleh diakses, dan halangan sosioekonomi secara signifikan mempengaruhi penjagaan dan hasil pesakit CKD. Selain itu, kajian itu menyerlahkan kelaziman masalah berkaitan ubat (DRP) yang tinggi dalam kalangan pesakit CKD. Hasilan dari intervensi oleh ahli farmasi klinikal menunjukkan. Penambahbaikan yang ketara terhadap rawatan yang diterima oleh pesakit. Hasil kajian ini mengaitkan peringkat CKD, polifarmasi dan intervensi oleh ahli farmasi sangat lah signifikan. Rumusan kajian ini menunjukkan beberapa factor yang penting dalam rawatan serta dapatan klinikal yang lebih baik bagi menyumbang kepada strategi pengurusan yang lebih baik dan penjagaan kualiti yang dipertingkatkan.

EXPLORING THE PERSPECTIVES ON THE MANAGEMENT AND EVALUATION OF THE IMPACT OF CLINICAL PHARMACIST INTERVENTION ON DRUG THERAPY PROBLEMS IN AMBULATORY PATIENTS WITH CHRONIC KIDNEY DISEASE: A MIXED-METHOD APPROACH

ABSTRACT

Chronic kidney disease (CKD) is the irreversible loss of normal kidney functions that is a slow and progressive disease. Chronic kidney disease is a widespread global health problem, yet there exists a notable gap in understanding the factors that shape treatment preferences according to the perspectives of patients and caregivers. The study aim was to conduct a novel qualitative study to explore the perspectives and experiences of patients and their carers' nephrologists, regarding the management of patients with CKD and to evaluate the prevalence of drug-related problems (DRPs) and the impact of clinical pharmacists on DRPs in ambulatory patients. A mixed-method study approach (qualitative and quantitative) was employed. A total of 11 nephrology experts and 19 CKD patients were included in the qualitative study. A descriptive phenomenological approach was used, entailing one-on-one semi-structured interviews to explore the perspectives and live experiences of nephrology experts and patients diagnosed with CKD. In the quantitative phase, a single-arm, pre and post-intervention study design was used. In this phase, the study population consisted of adult patients diagnosed with CKD stages 1 to 5 and undergoing treatment and follow-up at Khyber Teaching Hospital (KTH) and Medical Teaching Institution (DHQ), Bannu, patients were recruited during the study period from February 2022 to June 2022, and then from March 2022 to July 2022. Statistical

data analysis was performed using the Statistical Package for SocialSciences (SPSS) software program version 26 for Windows (SPSS, 2019). A 2-sided p-value < 0.05 was considered statistically significant. Exploring the nephrologist experts' perspectives regarding the CKD-affected population in Pakistan, they expressed that the majority of the people with CKD are between the ages of 40 and 60 years and those patients who have poor socioeconomic status are most likely prone to CKD. Nephrology experts consistently stated that diabetes, hypertension, and glomerulonephritis are the primary culprits and potential risk factors for CKD. Delayed referrals of patients with CKD were highlighted as a key barrier, a lack of accessible screening services, and the complexity of implementing a multidisciplinary care approach for CKD patients. CKD patients gave their perspectives and stated that illiteracy prevents them from reading and understanding the prescription labels of their medication. CKD patients stated that they experienced significant disruption and devastation in their lives due to the loss of employment, inability to work, affected businesses, and financial constraints and limitations they faced in purchasing medication. Overall, the barriers faced by nephrologists and patients are interlinked in the context of treatment for CKD. The findings of this study indicated a high prevalence of DRPs, with every patient experiencing at least one drug-related problem. The average number of drug-related problems (DRPs) per patient was determined to be 2.903 with a standard deviation of ± 1.148. The primary type of DRPs was found to be drug interaction 167 (45.1%) which was reduced to 76 (20.5%) after pharmacists intervened and statistically found significant (P= 0.032). Another common type of DRP was found to be poor compliance issues in the pre-intervention phase (n = 144 (38.9%) and reduced to 80 (21.6%) at post-intervention and observed statistically significant (P = 0.042). Untreated indications were found in 137 cases (37.0%);

however, with pharmacist intervention, this number was considerably reduced to 27 cases (7.3%) significantly (P = 0.004). The results of the multivariable logistic regression indicate that patients with CKD stage 3, eGFR (G3a 45 - 59 ml/min), are 8.838 (95% CI: 2.211 - 35.326) times more likely to have a prescription of wrong drugs compared to those with eGFR stage 1 (eGFR > 90 ml/min), with significant association (P = 0.002), Likewise, patients who were prescribed 7 to 8 distinct medications showed a significant association (P = 0.002) with the occurrence of DRPs, exhibiting odds ratios that were 14.272 times higher risk (95% CI: 2.650 - 76.871) when compared to individuals taking 1 to 2 medications. The key barriers such as delayed referrals, lack of accessible screening services, and socioeconomic barriers significantly influenced the care and outcomes of CKD patients. Moreover, the study highlighted the high prevalence of drug-related problems (DRPs) among CKD patients, with the interventions by clinical pharmacists showing promising results in mitigating these issues. Notably, CKD stages and polypharmacy emerged as significant predictors of DRPs, highlighting the importance of tailored interventions based on disease severity and medication regimen complexity. This study provides valuable insights for improving the care and outcomes of CKD patients, ultimately contributing to better management strategies and enhanced quality care for these patients affected by CKD.

CHAPTER 1

INTRODUCTION

1.1 Background of CKD

Chronic kidney disease (CKD) is a worldwide health problem. According to prognosis from the worldwide health observatory, at present it is one of the fast-rising causes of mortality globally (Angela C Webster et al., 2017). Throughout the world chronic kidney disease (CKD) affects patients. CKD is the irreversible loss of normal kidney functions that is a slow and progressive disease, (Vaidya & Aeddula, 2022). Chronic kidney disease (CKD) is a non-communicable health condition encompassing various physiological disorders associated with an abnormal kidney function and a progressive decrease in the glomerular filtration rate (GFR), (Ghojogh et al., 2017; Zeba et al., 2020).

Chronic kidney disease (CKD) has emerged as a significant contributor to mortality and the burden of disease in the 21st century. This increase is attributed, at least in part, to the growing prevalence of risk factors like obesity and diabetes mellitus. As a consequence, the number of individuals affected by CKD has been on the rise, affecting an estimated 843.6 million people worldwide in 2017, (Kitty J Jager et al., 2019).

1.2 Definition and classification of CKD

Chronic kidney disease (CKD) is a global public health issue, leading to severe consequences such as kidney failure, cardiovascular disease (CVD), and early death. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m2 for 3 months or more, irrespective of cause, Kidney damage in many

kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, ("KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)," 2017; Анемії, 2012).

CKD is also defined as ‘a progressive and irreversible condition, defined as an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 and/or kidney damage (haematuria or proteinuria) present for at least 3 months’, (Singh et al., 2013). Chronic Kidney Disease (CKD) is intricately linked to other significant health conditions, notably diabetes and cardiovascular disease, which persist as the primary contributors to both morbidity and untimely mortality within this patient population, (Lozano et al., 2012).

Chronic kidney disease is categorized into five stages, representing various degrees of kidney impairment, ranging from mild dysfunction to complete failure, (Ghojogh et al., 2017). Generally, individuals in stages 3 or 4 of CKD are considered to have moderate to severe kidney impairment. Stage 3 can be further divided into two sub-stages: 3b) with a GFR level between 45 to 59 ml/min/1.73 m2 and 3b) with a GFR level between 30 and 44 ml/min/1.73 m2. Stage 4 is characterized by a GFR of 15–29 ml/min/1.73 m2, (Ghojogh et al., 2017). As illustrated in Table 1.1, renal function progressively decreased from stage 1 to stage 5.

Table 1.1 Stages of chronic kidney disease (KDIGO, 2013)

GFR categories in CKD	GFR (ml/min/1.73 m^2)	Description
Stage 1	≥90	normal or high
Stage 2	60–89	mildly decreased
Stage 3a	45–59	mildly to moderately decreased
Stage 3b	30–44	moderately to severely decreased
Stage 4	15–29	severely decreased
Stage 5	<15	Kidney failure

Adapted from kidney disease: Improving Global Outcomes (KDIGO) CKD work group (2013); CKD-chronic kidney disease: GFR -glomerular filtration rate

Table 1.2 Classification of CKD based on albumin levels

Category	Description	Albumin excretion rate	Albumin -to creatinine ration
A1	Normal to mildly increased	<30 mg/g	<3 mg/mmol
A2	Moderately increased	30–300 mg/g	3–30 mg/mmol
A3	Severely increased	>300 mg/g	>30 mg/mmol

1.2.1 Risk factors for chronic kidney disease

Identifying factors that make an individual prone to CKD is crucial for both personal and community health. Certain risk factors are modifiable, and addressing them can help prevent or decelerate the progression to End-Stage Renal Disease (ESRD). Detecting and intervening early in individuals at risk of CKD can potentially prevent the onset and advancement of the disease. Diabetes mellitus (DM) stands as a recognized risk factor for CKD. Hypertension, which can be both a cause and consequence of CKD, has the potential to hasten renal disease progression towards End-Stage Renal Disease (ESRD), autoimmune disorders, chronic infections, malignancies, and genetic disorders, (Stevens & Levin, 2013).

Various sociodemographic factors heighten the risk of chronic kidney disease (CKD), encompassing factors like non-white race, limited education, low income, and food insecurity. These aspects highlight how certain social and economic conditions can influence the likelihood of developing CKD, (Banerjee et al., 2017; Inker et al., 2014).

1.2.2 Clinical presentation of chronic kidney disease

Chronic kidney disease is usually detected through regular screening involving serum chemistry profile and urine examinations, or it may be discovered incidentally. In some less common cases, patients might exhibit symptoms like visible blood in the urine, "foamy urine" (indicating the presence of albumin), frequent urination at night, pain in the flanks, or reduced urine output. In advanced CKD, patients may describe feelings of tiredness, loss of appetite, queasiness, vomiting, a metallic taste in the mouth, unintentional weight loss, itchiness, alterations in mental clarity, difficulty breathing, or swelling in the extremities, (Chen et al., 2019).

Typical laboratory findings in CKD patients include elevated levels of serum creatinine and blood urea nitrogen. Urine studies may reveal proteinuria (or albuminuria) and/or abnormal red or white blood cells under microscopic examination. Additionally, common laboratory abnormalities associated with CKD encompass anemia, hyperphosphatemia, hyperkalemia, metabolic acidosis, hypocalcemia, and increased parathyroid hormone (PTH). The prevalence of these abnormalities is contingent on the severity of CKD. Hyperphosphatemia is infrequent in CKD patients with an eGFR greater than 45 mL/min/1.73 m2. Conversely, PTH levels may exhibit a mild increase even with a slight reduction in eGFR (i.e., 50 to 60 mL/min/1.73 m2), (Fatehi et al., 2022).

1.2.3 Consequences of chronic kidney disease

Renal failure is regarded as the most severe consequence of chronic kidney disease (CKD),(Levey & Coresh, 2012). Additional consequences of chronic kidney disease (CKD) include the complications associated with a reduced glomerular filtration rate (GFR), an increased risk of cardiovascular disease (CVD), acute renal injury, cognitive impairment, infections, and impaired physical function, (Hsu et al., 2008; James et al., 2010; James et al., 2009; Wilhelm-Leen et al., 2009). Complications can arise at any stage of chronic kidney disease (CKD), potentially leading to fatal outcomes even in the absence of progression to kidney failure, (Levey & Coresh, 2012).

Chronic kidney disease impacts 8% to 16% of the global population and stands as a significant contributor to mortality. Effective management of CKD involves mitigating cardiovascular risk, addressing albuminuria, steering clear of potential nephrotoxins, and making necessary adjustments to drug dosages. Regular monitoring is essential for detecting complications associated with CKD, including hyperkalemia, metabolic acidosis, anemia, and other metabolic irregularities. Timely diagnosis, accurate staging, and the proper referral of CKD by primary care clinicians play a crucial role in alleviating the global burden of CKD.

1.3 Global burden of CKD

Chronic kidney disease (CKD) is now a global public health issue, primarily because of its rising occurrence, the risk of progressing to end-stage kidney disease, and its substantial impact on people's health and risk of death, (Vos, 2020).The global burden of CKD is anticipated to persistently rise due to the escalating prevalence of diabetes, the foremost cause of CKD on a global scale. A substantial portion of this

growing burden is foreseen in the Asian region, encompassing more than 4.5 billion individuals, which constitutes 60% of the world's population, (Jha et al., 2013; Liyanage et al., 2015). The occurrence of CKD, particularly in developing nations, is on the rise, as reflected by the disability-adjusted life years (DALY) for CKD, which nearly doubled from 0.8 in 1990 to 1.6 in 2019, (García et al., 2022; Vos, 2020).

The prevalence of CKD and end-stage renal disease (ESRD) is increasing globally. The estimated prevalence of CKD in the US was 16.8% while in Asia the prevalence ranged from 12.1% to 17.5% (Centers for Disease Control and Prevention, 2007; Ingsathit et al., 2010). The prevalence of CKD in the general population, as reported primarily from urban areas of South Asia, has ranged from 7.2% to 17.2% (Alam et al., 2014; Singh et al., 2013). The Centres for Disease Control and Prevent reported that the ninth leading cause of death in the United States is kidney disease, (Control & Prevention, 2015).

1.4 Prevalence of CKD in South Asia

South Asia, in particular, is projected to witness a remarkable increase in diabetes prevalence, estimated to exceed 150% between 2000 and 2035 (Guariguata et al., 2014; Nanditha et al., 2016). Additionally, South Asian nations are going through an epidemiological transition with a rise in CKD risk factors, which is burdening their health systems (Jafar et al., 2013). In Asia, approximately 434.3 million adults were affected by chronic kidney disease (CKD), of which 65.6 million had advanced CKD (Liyanage et al., 2022).

Chronic kidney disease (CKD) is on the rise in South Asian nations such as Pakistan, and the causes are multifaceted. Most people have insufficient health-care provision due to a lack of health education, a lack of primary healthcare, insufficient government funding, and, most significantly, the increasing prevalence of CKD risk factors such as diabetes and hypertension. Other reasons, such as glomerulonephritis and renal stones, are also common as a result of infections and dry weather, (Jafar, 2006). The importance of patient-centered care, research, and policy are now generally acknowledged. This method necessitates a thorough knowledge of the beliefs, values, and experiences of patients with chronic kidney disease (CKD) and their families, which are not always communicated in clinical settings. In health care, qualitative approaches are used to generate hypotheses and theories to describe social and experiential phenomena, (Giacomini et al., 2000).

The physical health of patients is at risk due to chronic kidney disease (CKD), which also has a significant adverse effect on their everyday lives, bringing about substantial adjustments on both a mental and psychological level. This condition poses a serious threat to worldwide public health, and the number of people with CKD is steadily rising (Kefale et al., 2019; Oh et al., 2019; Sanyaolu et al., 2019). CKD is one of the world's fastest growing causes of death, with a larger burden in low- and middle-income countries (LMICs) than in high-income countries (Katherine T Mills et al., 2015; Stanifer et al., 2016). In South Asia, the number of people with diabetes is expected to surge by more than 150% from 2000 to 2035. Moreover, China and India are forecasted to maintain their positions as the countries with the largest diabetic populations by 2035, with a combined total of 251.7 million individuals affected, (Guariguata et al., 2014; Nanditha et al., 2016). These data suggest that there is a growing problem of chronic kidney disease (CKD) in Asia. In other words, more and

more people in Asia are being affected by CKD, and this is becoming a significant health issue in the region.

1.4.1 Epidemiology of chronic kidney disease in a Pakistani population

Pakistan is a rapidly expanding nation, currently boasting a population of 207 million, and experiencing an annual growth rate of 2.7 percent. Projections indicate that if this growth rate continues, the population could reach 330 million by the year 2030, (Bongaarts, 2020). Chronic kidney disease (CKD) is on the rise in South Asian nations such as Pakistan, and the causes are multifaceted. Most people have insufficient health-care provision due to a lack of health education, a lack of primary healthcare, insufficient government funding, and, most significantly, the increasing prevalence of CKD risk factors such as diabetes and hypertension. Other reasons, such as glomerulonephritis and renal stones, are also common as a result of infections and dry weather, (Jafar, 2006). The annual incidence of new end-stage renal disease (ESRD) cases in Pakistan is estimated to exceed 100 per million population, (Jafar et al., 2005). In a study examining the epidemiology of chronic kidney disease (CKD) in Pakistan, Jafar et al. reported the highest prevalence at 29.9%, while Jessani et al. reported the lowest prevalence at 12.5% within the same institute and age group. The overall prevalence of CKD across all age groups was determined to be 21.2%, (Imtiaz & Alam, 2023).

Chronic Kidney Disease (CKD) poses a significant strain on the healthcare resources in Pakistan. The absence of systematic screening and risk assessment frequently leads to delays in treatment and the execution of preventive interventions. Consequently, this delay commonly culminates in the development of End-Stage Renal Failure (ESRD), necessitating the utilization of kidney transplantation and

dialysis therapies, (Yaqub et al., 2013). There is a significant impact of CKD on Pakistan's healthcare system, delays in treatment and implementation of preventive steps are frequently caused by a lack of screening and risk identification (Shcherbak et al., 2013; Yaqub et al., 2013).

It is also believable that the higher prevalence of hypertension, diabetes, and smoking among the younger population in Pakistan is contributing to a higher incidence of CKD in this age group, (Alam et al., 2014; Gilani & Leon, 2013). According to a recent study, the incidence of CKD is greater in individuals under the age of 50 in Pakistan, and the leading causes of CKD include glomerulonephritis, diabetic nephropathy, renal stones, and hypertension, (Ullah et al., 2015). However, more research is needed to evaluate both these aspects since there is insufficient reliable evidence.

1.5 Pharmacotherapy interventions in chronic kidney disease management

1.5.1 Prevention and treatment of CKD

A graded, inversely proportional link exists between cardiovascular disease (CVD) risk and glomerular filtration rate (GFR), and this connection remains unrelated to age, gender, and other recognized risk factors, (Consortium, 2010).

As a result, it is vital to manage established risk factors, including diabetes mellitus, hypertension, obesity, and metabolic syndrome, and to use suitable antiplatelet therapy in order to decrease cardiovascular risks. The prevention of cardiovascular disease (CVD) primarily relies on medications, which are frequently prescribed for long-term use, including lipid-lowering drugs, blood pressure medications, and oral antidiabetic agents. Consequently, there is an elevated risk of

toxicity associated with inappropriate medication dosages (IMD), (Ministry of Health Malaysia, MaHTAS, 2018).

Given the substantial burden of comorbidities in CKD patients and the complexity of their medication regimens, effective management necessitates the collaborative efforts of a multidisciplinary team comprising nephrologists, endocrinologists, primary care physicians, nurses, dietitians, and pharmacists (Joy et al., 2005). The implementation of strategies to enhance medication therapy management through clinical pharmacist services has the potential to make a substantial contribution to the multidisciplinary team, ensuring safe, effective, and cost-effective care for ambulatory patients with CKD (Al Raiisi et al., 2019).

There is a significant impact of CKD on Pakistan's healthcare system, delays in treatment and implementation of preventive steps are frequently caused by a lack of screening and risk identification, (Yaqub et al., 2013). Qualitative research enables access into in-depth insights about patients' priorities, values, and beliefs (Reeves et al., 2008) and is becoming more common in clinical and health services research, especially in the areas of palliative care, oncology, primary care, and mental health, (McKibbon & Gadd, 2004).

There are several challenges associated with CKD management, such as the lack of awareness among the general population about the risk factors and preventive measures for CKD, limited access to CKD screening and diagnostic tools, and the high cost of treatment. Nephrologists and nephrology clinicians play a critical role in addressing these challenges. However, their perspectives and experiences regarding CKD may influence their ability to provide optimal care for their patients. By identifying the challenges faced by these healthcare professionals and addressing their

concerns, Policymakers can develop strategies to improve CKD management and ultimately reduce the burden of CKD on individuals and society. Overall, a better understanding of the perspectives and experiences of nephrologists and nephrology clinicians regarding CKD can help improve the quality of care provided to patients with this disease and ultimately improve patient outcomes. Understanding patients' experiences of communicating with and getting information from renal clinicians is crucial in clinical practice and staff education, and to ensure equity in the management of CKD. Therefore, it was paramount important to explore perspectives both nephrology experts and post nephrology residents and experiences of communication and information provision, treatment seeking behavior and satisfaction regarding chronic kidney disease among population with CKD.

Understanding the experiences and perceptions of CKD patients is crucial to improving their quality of life and providing more effective support. However, there is limited research conducted on CKD patients' perspectives and experiences. Qualitative research has the potential to provide valuable insights into the lived experiences of CKD patients, including their physical, emotional, and social challenges. Therefore, the problem statement is to explore the feasibility and effectiveness of conducting qualitative research in CKD patients to gain insights into their experiences, perceptions, and perspectives. Specifically, this research seeks to explore the challenges, coping strategies, and needs of CKD patients from their own perspectives. By exploring the comprehensive literature, it was concluded that chronic kidney disease (CKD) is a complex and prevalent medical condition that requires specialized care, particularly in the outpatient settings. Nephrologists and senior nephrology residents, are the key stakeholders in CKD management and possess exclusive insights and experiences, and perspectives that can significantly impact

patient health outcomes. So, there is a scarcity and limited understanding of their viewpoints, perspectives and experiences in treating and managing CKD patients at outpatient nephrology departments. Therefore, the professional problem at hand is to, explore and delve into the perspectives and live experiences of nephrologists and nephrology residents and analyse concerning CKD treatment and management at outpatient nephrology departments.

However, there is a dearth of representative data on the qualitative research exploring the real-world experiences of nephrologists and nephrology clinicians to learn their perspectives on the affected population, their familiarity with CKD diagnosis, treatment, and management, the obstacles they face when trying to diagnose CKD, and their ideas for advancing the state of CKD care.

1.5.2 The prescription pattern of medication

The prescription patterns vary among different treating physicians, disease conditions, and patient populations, underscoring the significance of studying drug utilization over a specific time frame, (Ahlawat et al., 2015). Conducting prescribing pattern studies in chronic kidney disease (CKD) can facilitate the identification of potential modifications in prescribing practices to enhance the appropriateness and wisdom of medical care. The appropriate selection of treatment in healthcare is a dynamic process that requires continuous monitoring, evaluation, and collaboration between healthcare professionals and patients. The careful selection of treatment ensures optimal benefits for patients while minimizing the occurrence of drug-related problems (DRPs), (Minutolo et al., 2008).

As the kidneys are responsible for eliminating numerous drugs from the body, dosage adjustments may be necessary for patients with renal impairment. It is crucial to optimize and monitor the dosing of all drugs, including antibiotics, in order to prevent adverse drug reactions, prevent additional renal damage, and improve treatment outcomes, (Decloedt et al., 2010; Markota et al., 2009). The existence of multiple comorbidities and disease complications, coupled with suboptimal adherence to medication, frequent dosage adjustments, and a high number of prescribed medications, can increase the risk of drug-related morbidity and associated problem, (Emami et al., 2012; St Peter et al., 2013). The use of multiple concurrent medications has been demonstrated to negatively impact medication adherence in CKD patients, potentially resulting in disease progression and increased rates of rehospitalization (Mechta Nielsen et al., 2018).

1.6 Drug-related problems in CKD patients

Patients with chronic kidney disease (CKD) are more likely to experience substantial buildup of drugs that are excreted by the kidneys, this situation could elevate the potential for severe or permanent harm. Moreover, administering medications at incorrect dosages to CKD patients can result in adverse outcomes, including illness, extended hospital stays, and potentially even fatalities. Medications that are excreted through the kidneys and have a narrow range between safe and toxic levels, such as digoxin or lithium, raise the chances of toxicity. In specific instances, accumulation takes place gradually over several weeks, and the symptoms of toxicity may develop gradually, (Lea-Henry et al., 2018; Miners et al., 2017).

The landmark article by Helper and Strand (1990) defined drug related problem (DRP) as:

> *"An event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care"*

The term "problem" in this meaning refers to a specific drug-related event that is susceptible to detection, treatment, or prevention. A DRP is an occurrence that meets the following two criteria:(1) a patient must be experiencing or must be likely to experience symptoms and (2) these symptoms must have an identifiable or suspected relationship with drug therapy (Hepler & Strand, 1990).

1.6.1 Classification of drug related problems

The classification of DRPs is given below and was compiled according to a modified version of (Hepler & Strand, 1990).

1. The need for an additional drug
2. Unnecessary drug
3. Non-optimal drug, including drug formulation
4. Non-optimal dosing, including optimal dosing schedule
5. No further need for the drug
6. Drug–drug interactions
7. Need for laboratory tests [e.g. therapeutic drug monitoring (TDM), laboratory values, microbiology.
8. Adverse effects (being experienced) (ADRs)
9. Medical chart error (e.g. dose not stated)
10. Compliance problems

11. Patient education required (giving patient information on the physicians request, e.g. to avoid non-compliance)
12. Information/therapy discussion (regarding a specific drug regimen for a patient)
13. Others

In addition to Drug-Related Problems (DRPs), various terms have been utilized to characterize issues associated with the use or outcomes of medications. These terms include drug therapy problem, medicine- or medication-related problem, pharmacotherapy failure, drug treatment failure, negative clinical outcome related to medicine, and treatment-related failure (AbuRuz et al., 2006; de Granada, 2007; van Mil et al., 2004).

Patients with CKD often receive suboptimal treatment, which is linked to a higher risk of progressing to end-stage renal disease (ESRD). Additionally, most CKD patients have comorbidities like electrolyte abnormalities, cardiovascular issues, and mineral bone disorders, leading to complex medication regimens, (St Peter et al., 2003; Tonelli et al., 2015). These factors could potentially heighten the likelihood of experiencing drug-related issues (DRPs), such as adverse drug reactions (ADRs), interactions between medications, and improper dosing and monitoring of blood chemistry. As a result, significant levels of illness, mortality, and healthcare expenses can occur, (Belaiche et al., 2012; Lalonde et al., 2017). The simultaneous use of multiple medications has been demonstrated to hinder medication adherence among CKD patients, potentially resulting in disease progression and the need for rehospitalization, (Cohen et al., 2020; Mechta Nielsen et al., 2018).

Multiple factors can contribute to drug-related morbidity and medication-related problems (MRPs) such as a large number of prescribed medications due to comorbidities and complications associated with the disease, suboptimal medication adherence, and frequent changes in dosages, (Manley et al., 2005; St Peter et al., 2013). Medication reconciliation, carried out in collaboration with other healthcare providers, is an important approach that clinical pharmacists can employ to identify medication-related problems, (Raimbault-Chupin et al., 2013).

Pharmacists have become an essential component of the multidisciplinary team providing clinical care to patients across diverse healthcare settings. Evidence suggests that their interventions in outpatient, inpatient, and emergency department settings are associated with improved outcomes related to treatment-related problems and reductions in hospitalizations and mortality, (Basheti et al., 2019). The role of pharmacists has progressed beyond the mere dispensation of medications to encompass more patient-centered services, such as providing pharmaceutical care. This includes identifying, preventing, and resolving medication-related problems (MRPs) to improve patient outcomes, (Chua et al., 2012). The intervention of pharmacists in optimizing prescriptions is crucial in preventing adverse drug reactions (ADRs) and reduced treatment efficacy, which are critical for ensuring the safe and effective use of pharmacotherapy. By analyzing routine pharmaceutical interventions, clinical pharmacists can detect potential medication-related problems (MRPs) and improve prescriptions by making necessary optimizations based on their findings. This can lead to improved patient outcomes and the promotion of safe and effective pharmacotherapy, (Tasaka et al., 2018).

There has been a lack of research into the causes and consequences of CKD in Pakistan, and just a few of studies have been conducted in hospitals. CKD of unknown aetiology, glomerulonephritis, and kidney stones were more common in rural areas, while CKD caused by diabetes mellitus (DM) and hypertension (HTN) was more common in urban areas (Rizvi & Manzoor, 2002; Salman et al., 2017).

1.7 Role of clinical pharmacist in managing DRPs

In Pakistan, the impact of clinical pharmacists in reducing drug-related problems was assessed through a prospective, interventional study conducted at a teaching-based hospital. The study aimed to identify drug-related problems and their underlying causes. Among the 161 recommendations provided by clinical pharmacists, 86.33% (n=139) were successful in resolving the identified problems, while 6.83% of the recommendations were considered ineffective as they did not adequately address the respective issues. The findings of this study provide evidence that clinical pharmacists play a crucial role in hospital activities and can significantly enhance the quality of medication use and patient safety. Furthermore, the study highlights the high acceptance of clinical pharmacist intervention by prescribers and demonstrates the positive contribution of clinical pharmacists in identifying and addressing drug-related problems in the healthcare setting of Pakistan, (Khan & Ahmad, 2014).

Clinical pharmacists collaborate closely with both physicians and patients to ensure that prescribed medications yield the most effective therapeutic outcomes for patients. A crucial responsibility of pharmacists is to diligently monitor drug therapy and provide recommendations to physicians regarding appropriate dosages and dosage intervals, (Anggriani et al., 2018).

To improve patient outcomes, the clinical pharmacist is actively involved in various clinical activities within the hospital and plays a crucial role in optimizing medication use and promoting patient safety (Khan & Ahmad, 2014). The clinical pharmacist's role in promoting optimal medication usage is crucial, as they work to ensure that patients receive appropriate pharmacotherapy, thereby minimizing the potential for adverse outcomes associated with medication usage, (George et al., 2015). The intervention of a clinical pharmacist has a substantial impact on patient care across multiple hospital settings. Through drug therapy optimization, prevention of adverse drug events, and patient education, they play a critical role. Moreover, their involvement in designing macro processes aimed at minimizing the risk of medication-related errors and implementing specific medication interventions is crucial for ensuring medication safety, (Dunn et al., 2015).

Overall, the integration of clinical pharmacists in healthcare settings in developing countries like Pakistan is essential to enhance the quality and safety of patient care, optimize medication use, and address healthcare disparities. Their expertise and active involvement can lead to improved health outcomes and better management of health resources in challenging healthcare environments. DRPs in the outpatient settings of a of hospitals am was to identify and address DRPs to optimize the patient's medication therapy and improve their overall health outcomes.

In addition to developed countries, Nepal and Indonesia have also integrated clinical pharmacists into their clinical settings, which may have contributed to a reduction in medication dosing errors. Consequently, we suspect that the absence of clinical pharmacists and computerized dose adjustment programs in Pakistani clinical settings could be a contributing factor to higher medication dosing errors. Furthermore, in our study setting, higher medication dosing errors may have been influenced by

various other factors, including physician negligence and adherence to traditional clinical practices, insufficient laboratory support, and the absence of standardized dosing guidelines (Salomon et al., 2003; Sweileh et al., 2007). Chronic kidney disease (CKD) poses detrimental effects, especially in developing nations, such as end-stage renal disease (ESRD), progressive cardiovascular disease (CVD), increased mortality at an early stage, and significant morbidity, (Gansevoort et al., 2013; Jha et al., 2012). Furthermore, the selling of counterfeit drugs is a $30 billion worldwide economy, and in some LMICs, counterfeit drugs may account for 10 to 60% of the drug market. These uncontrolled substances may not only be a major cause of CKD in LMICs, but people with CKD may be especially susceptible to their adverse effects (Mackey et al., 2015).

1.8 Mixed methods

Mixed methods research has emerged as a third methodological approach, evolving over nearly thirty years. It began following the so-called 'paradigm wars' of the 1980s. (Teddlie & Tashakkori, 2009). Mixed Methods research integrates both qualitative and quantitative research methods to enhance the study's potential. While it has its own philosophical foundations, data collection follows the procedures specified by each respective methodology. Depending on the research design, the mixing and interpretation of different data occur either throughout the study or at the end of the study (Creswell, 2009). Mixed methods research creatively integrates elements of both quantitative and qualitative methodologies within a single study. It emerged as a practical solution for addressing scientific questions that cannot be adequately answered by using only one methodology, (Plano Clark, 2017).

According to Tashakkori and Creswell (Tashakkori & Creswell, 2007), mixed methods research is defined as "research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or program of inquiry. When combined with mixed methods, action research can yield more scientifically robust and transferable results by synergistically integrating qualitative stakeholder engagement methods with quantitative outcome-based approaches, (Ivankova, 2015; Ivankova, 2017).

The main aim of a mixed-methods research design is to achieve a more comprehensive and deeper understanding by offering a fuller picture that enhances the description and comprehension of phenomena. Mixed-methods research has gained popularity because it combines quantitative and qualitative data within a single study, providing stronger inferences than using either approach alone. In other words, a mixed-methods paper helps to understand the holistic picture by integrating meanings obtained from interviews or observations with the prevalence of traits in a population obtained from surveys, thus adding both depth and breadth to the study, (Creswell, 2014).

A small number of qualitative studies have been conducted to investigate the disease-related experiences of individuals with co-morbid diabetes and CKD, (Sakraida & Robinson, 2009; Williams et al., 2009), but none have explored patients' perspectives and experiences on the important factors affecting optimum health-care such as understanding of the disease (CKD), treatments seeking behaviour, patients understanding towards treatment, patients evaluation of medication adherence and patients satisfaction through semi-structure interviews. Subsequently, in this novel qualitative study, we explored the perspectives and experiences of patients and their

carers nephrologists and nephrology postgraduates' residents on the factors that influence their health-and health care of those with co-morbid conditions and chronic kidney disease (CKD.

In a quantitative study on CKD, research investigates questions regarding the efficacy of interventions, prognosis, and the strength of associations between risk factors and outcomes. The elimination of numerous drugs by the kidneys may necessitate dose adjustments in patients with renal impairment, and the administration of all drugs, including antibiotics, should be optimized and monitored to prevent adverse drug reactions, prevent further renal injury, and improve treatment outcomes (Decloedt et al., 2010; Markota et al., 2009).

1.9 Problem statement

Multiple factors contribute to the rise of chronic kidney disease (CKD) in south Asian nations like Pakistan. Most people do not receive proper care because of a number of problems, including a lack of health education, a lack of primary health care, a lack of government funding, and, most critically, the rising incidence of risk factors for CKD such as diabetes and hypertension. Infections and arid climates also contribute to a rise in kidney problems such as glomerulonephritis and renal stones, (Jafar, 2006). Understanding the patient's perspective, values, and priorities is essential for share decision-making and collaborative treatment approaches. By uncovering patients' preferences for care, qualitative research methods could influence practice and policy based on a deeper understanding of patients' experiences, values, and priorities, (Tinetti et al., 2016).

My rigoruos investigation into nephrology clinician's experiences and perspectives regarding the treatment provided to the patients with CKD, arise from the concerns regarding the difficulties in providing and receiving the care, availability of nephrologists, timely referral issues of the patients to the nephrologists, limited availability of resources, and communication by CKD patients deficits in health care infrastructure including lack of preventive care, difficulties affording CKD treatment, refusals of the CKD diagnosis, CKD treatment by practitioners of alternate medicine, and poor quality of life leading to worse condition, the time when the patients visit the outpatient nephrology department, (Anees et al., 2018; Narva et al., 2016; Tam-Tham et al., 2016).

A substantial body of literature has demonstrated that patients' illness perceptions of kidney failure are linked to various outcomes, including depression, health-related quality of life (HRQOL), and mortality, (Parfeni et al., 2013). To date, few studies have concentrated on the earlier stages of chronic kidney disease (CKD). However, the longitudinal research conducted indicates that strong negative illness perceptions are prevalent and serve as a marker for poor outcomes, (Muscat et al., 2020).

Moreover, studies have demonstrated that unhelpful illness perceptions can be altered through psychoeducational support strategies, resulting in improved coping behaviors and better health outcomes, (Alyami et al., 2021). Therefore, identifying unhelpful illness perceptions could provide unique opportunities to enhance patient-reported and clinical outcomes before kidney failure occurs. Currently, routine nephrology care lacks tools to identify and support patients with unhelpful illness perceptions. To develop adequate, timely, and personalized assessment and support tools, an in-depth understanding is required of the illness perceptions underlying

patients' personal experiences and their ability to cope with CKD, as well as how these perceptions evolve over time. Additionally, understanding stakeholders' needs regarding illness perception-based tools is essential, (Meuleman et al., 2024).

Patients with CKD rely on time-consuming and invasive treatments with rigid schedules, managing numerous symptoms, complications, and unpredictable events that can hinder their capacity for involvement, (Banerjee et al., 2020; Finderup et al., 2021). Caregivers also have significant responsibilities, which may further limit their ability to participate in research. These burdens exacerbate the challenges of identifying and navigating research systems. There is limited evidence regarding the perspectives of CKD patients and their caregivers on research participation (Banerjee et al., 2020). Few data exist on the actual management of patients with CKD in ambulatory care, particularly with regards to monitoring and management of risk factors and nephrologist referral, despite the fact that the majority of patients with CKD are cared for ambulatory care. When formulating and enforcing healthcare policy and guidelines for CKD, it is crucial to conduct an in-depth analysis of the current state of care in order to pinpoint problematic areas and prioritize their resolution, (Peters et al., 2022).

To the best of our knowledge, no novel qualitative studies have been conducted that explore the perspectives and experiences of ambulatory patients living with chronic kidney disease (CKD) and their caregivers, as well as nephrologists and nephrology postgraduate residents. Specifically, there is a lack of research focusing on the factors that influence their health and the nephrological care of CKD and comorbid conditions with CKD within the outpatient nephrology department in this particular region. This includes the community of Khyber Pakhtunkhwa (KPK), Pakistan. This study aims to fill this gap by providing insights into the unique challenges and barriers

faced by this population, which can ultimately inform better care practices and health outcomes for CKD patients in this region.

With regard of quantitative study, in low-income nations, chronic kidney disease (CKD) is contributed by various factors such as infectious diseases, indigenous medicines, environmental and industrial pollution, and dietary factors. Although diabetes mellitus (DM) and hypertension (HTN) are globally recognized as the primary causes of CKD, these additional factors play significant roles in contributing to the disease burden in low-income nations. Tracing the origins of chronic kidney disease (CKD) in low-income nations is particularly challenging due to the diverse local populations. These populations exhibit significant variations in economic development, ethnic composition, rural-urban divide, wealth inequality, and access to medical care when compared to developed countries. Consequently, pinpointing the specific community that requires special precautions becomes difficult, leading to challenges in extrapolating preventive measures to this group, (Jha et al., 2013; Weaver et al., 2015). As a result, it is challenging for public health leaders and policy makers to develop effective strategies to reduce CKD-related mortality and morbidity without having a full picture of the CKD burden in these nations. In a developing country like Pakistan, the presence of clinical pharmacists is of utmost importance to bridge the existing gap in healthcare settings within the nation, (Aslam & Ahmed, 2011; McNatty et al., 2007).

Integrating clinical pharmacists can enhance the quality and safety of care, and optimize medication use, leading to improved health outcomes and better management of limited resources and its imperative to conduct additional research specifically focused on investigating the prevalence and clinical significance of DRPs in CKD patients residing in this particular region. Thus, due to the inherent variations in