THE STUDY OF CLINICAL OUTCOMES AND FACTORS AFFECTING DRUG THERAPY AND OSTEOPOROTIC CONDITION IN CHRONIC KIDNEY DISEASE (CKD) PATIENT IN THREE TERTIARY HOSPITALS IN PAKISTAN

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by

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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACE-I	Angiotensin Converting Enzyme Inhibitors
ACR	Albumin-to-creatinine ratio
AER	Albumin Excretion Rate
AHRQ	Agency for Healthcare Research and Quality
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
ARB	Angiotensin Receptor Blockers
BLR	Binary Logistic Regression
BMD	Bone Mineral Density
BMI	Body Mass Index
CDC	Centre for Disease Control
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-KAP	Knowledge, Attitude and Practice of Chronic Kidney Disease
CME	Continuing Medical Education
COPD	Chronic Obstructive Pulmonary Disease
CRF	Chronic Renal Failure
DALY	Disability Adjusted Life Years
DXA	Dual energy x-ray absorptiometry

EFA	Exploratory Factor Analysis
ESA	Erythropoietin Stimulating Agents
ESRD	End Stage Renal Disease
FN	Femoral Neck
GFR	Glomerular Filtration Rate
IRT	Item Response Theory
IV	Intravenous
JNC	Joint National Commission
KAP	Knowledge, Attitude and Practices
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KMO	Kaiser-Meyer-Olkin
LS	Lumbar Spine
MBBS	Bachelor of Medicine, Bachelor of Surgery
MBD	Mineral and Bone Disorder
MDRD	Modification of Diet in Renal Disease
MSA	Measure of Sampling Adequacy
NCD	Non-communicable Diseases
NKF	National Kidney Foundation
NSKH	Nawaz Sharif Kidney Hospital
PG	Post-graduate
Pharm D	Doctor of Pharmacy
PIMS	Pakistan Institute of Medical Sciences

PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
PTH	Parathyroid Hormone
RAAS	Renin Angiotensin Aldosterone System
SD	Standard Deviation
SDG	Sustainable Development Goals
SPSS	Statistical Package for Social Sciences
TH	Total Hip
UN	United Nations
WHO	World Health Organization

KAJIAN HASIL KLINIKAL DAN FAKTOR YANG MEMPENGARUHI TERAPI UBAT DAN KEADAAN OSTEOPOROTIK DALAM KALANGAN PESAKIT KEGAGALAN RENAL KRONIK DI TIGA HOSPITAL TERTIARI DI PAKISTAN

ABSTRAK

Penyakit Buah Pinggang Kronik (CKD) dikaitkan dengan beberapa komplikasi termasuk osteoporosis. Kajian ini bertujuan untuk menentukan prevalens osteoporosis dan hasil klinikal bersama dengan pengetahuan, sikap dan amalan (KAP) doktor dan ahli farmasi. Kajian kuantitatif prospektif termasuk kajian keratan rentas dan membujur digunakan untuk memenuhi objektif. 196 dan 412 pesakit CKD telah dikaji untuk menentukan prevalens osteoporosis dan hasil klinikal masing-masing. KAP 400 doktor dinilai menggunakan soal selidik CKD-KAP yang telah dibangunkan dan disahkan. Pengetahuan mengenai CKD juga ditentukan dalam kalangan 183 ahli farmasi. Prevalens osteoporosis dan osteopenia didapati masing-masing 26.5% dan 40.8%. Pengurangan sebanyak 0.58% dalam eGFR diperhatikan menyumbang kepada hasil klinikal yang lemah. Pesakit lelaki menunjukkan tindak balas yang lebih baik terhadap terapi dan hipertensi kekal sebagai faktor risiko yang paling biasa dan dikaitkan dengan hasil yang buruk ($p < 0.05$). Purata peningkatan eGFR sehingga 29.09% diperhatikan dengan penggunaan antihipertensi dan antaranya, penghalang beta dikaitkan dengan hasil yang lebih baik ($p < 0.05$). Hiperkalemia dan hypoalbuminemia diperhatikan dalam kalangan majoriti pesakit CKD, dan kedua-duanya dikaitkan dengan hasil yang buruk ($p < 0.05$). Ketumpatan Mineral Tulang (BMD) bertambah baik sebanyak 7.83% menunjukkan hasil

yang lebih baik untuk keadaan osteoporosis. eGFR mempunyai korelasi positif dengan skor BMD T. Permulaan awal kalsium yang mengandungi pengikat fosfat dan analog vitamin D dikaitkan dengan BMD yang lebih tinggi. CKD-KAP telah disahkan di kalangan 100 pakar perubatan dan alat itu didapati sah dan boleh dipercayai dari segi psikometrik. Purata pengetahuan pakar perubatan ialah 61.86% yang dikaitkan secara langsung dengan pengalaman klinikal. Purata peratus sikap positif ialah 55.56%, dengan pengetahuan, umur dan pengalaman klinikal merupakan pembolehubah yang paling ketara berkaitan ($p < 0.05$). Purata amalan positif keseluruhan ialah 82.19%, dengan sikap doktor merupakan pembolehubah yang paling ketara berkaitan ($p < 0.05$). Antara ahli farmasi yang dikaji, 50.9% mempunyai pengetahuan yang baik, dengan lelaki dan ahli farmasi dari kumpulan umur yang lebih tinggi dan pengalaman klinikal mempunyai pengetahuan yang lebih baik ($p < 0.05$). Disimpulkan bahawa terdapat prevalens osteoporosis yang tinggi di kalangan pesakit CKD di Pakistan yang tidak diurus dengan betul, yang membawa kepada hasil yang buruk. Amalan pengurusan osteoporosis adalah mencukupi namun penambahbaikan selanjutnya boleh meminimumkan risiko fraktur tulang spontan. Pengetahuan pakar perubatan dan ahli farmasi terhadap CKD adalah agak rendah dan pihak berkuasa kesihatan dan pembuat dasar harus mengambil langkah yang perlu untuk meningkatkan pengetahuan dan amalan untuk meningkatkan hasil klinikal.

THE STUDY OF CLINICAL OUTCOMES AND FACTORS AFFECTING DRUG THERAPY AND OSTEOPOROTIC CONDITION IN CHRONIC KIDNEY DISEASE (CKD) PATIENT IN THREE TERTIARY HOSPITALS IN PAKISTAN

ABSTRACT

Chronic Kidney Disease (CKD) is associated with several complications including osteoporosis. This study was aimed to determine prevalence of osteoporosis and clinical outcomes along with knowledge, attitude and practices (KAP) of physicians and pharmacist. Prospective quantitative research including cross-sectional and longitudinal study was used to meet the objectives. 196 and 412 CKD patients were studied to determine the prevalence of osteoporosis and clinical outcomes respectively. The KAP of 400 physicians was assessed using CKD-KAP questionnaire which was developed and validated. The knowledge regarding CKD was also determined among 183 pharmacists. Prevalence of osteoporosis and osteopenia was found to be 26.5% and 40.8%, respectively. A reduction of 0.58% in eGFR was observed accounting to poor clinical outcomes. Male patients show better response to the therapy and hypertension remained the most common risk factor and was associated with poor outcomes ($p < 0.05$). Mean eGFR improvement up to 29.09% was observed with the use of antihypertensives and among them, beta blockers were associated with better outcomes ($p < 0.05$). Hyperkalemia and hypoalbuminemia were observed among majority of CKD patients, and both were associated with poor outcomes ($p < 0.05$). The Bone Mineral Density (BMD) improved by 7.83% indicating better outcomes for osteoporotic conditions. eGFR had a positive correlation with BMD T score. Early initiation of calcium containing phosphate binders

and vitamin D analogues was associated with higher BMD. CKD-KAP was validated among 100 physicians and the tool was found to be psychometrically valid and reliable. The average knowledge of physicians was 61.86% which was directly associated with clinical experience. The mean percent positive attitudes were 55.56%, with knowledge, age and clinical experience being the most significantly associated variables ($p < 0.05$). The overall mean positive practices were 82.19%, with physicians' attitude being the most significantly associated variable ($p < 0.05$). Among the studied pharmacists, 50.9% had good knowledge, with males and pharmacist from higher age group and clinical experience had better knowledge ($p < 0.05$). It was concluded that there is high prevalence of osteoporosis among the CKD patients in Pakistan which are not properly managed, leading to poor outcomes. The practices of management of osteoporosis are adequate however further improvements can minimize the risk of spontaneous fractures. The knowledge of physicians and pharmacist towards CKD is relatively low and health authorities and policy makers should take necessary measures to enhance the knowledge and practices to improve clinical outcomes.

CHAPTER 1
INTRODUCTION

1.1 Chronic Kidney Disease

Chronic kidney disease (CKD) or chronic renal failure (CRF) represents a kidney disorder characterized by kidney damage, reduced kidney function and a reduction of glomerular filtration rate (GFR) to less than 60 mL/min for three months or more. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio of greater than 30 mg/g in two of three spot urine specimens. GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft-Gault formula. Kidney disease severity is classified into five stages according to the level of GFR. (Parmar, 2002; A. S. Levey et al., 2005; Delanaye & Mariat, 2013).

Kidney failure is a worldwide public health problem, with increasing incidence and prevalence, high costs, and poor outcomes. (Eknoyan et al., 2004; Eckardt et al., 2013) The prevalence of CKD is estimated to be 8–16% worldwide but individual data of each country should be determined separately for better understanding of the risk. Causes and risk factors in individual countries should be determined to implement better prevention and control strategies. Awareness of the disorder, however, remains low in many communities and even among many physicians. (Jha et al., 2013)

1.2 Stages of CKD

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) have

recommended to classify CKD based on GFR and albuminuria category. (Andrassy, 2013; Levin et al., 2013)

1.2.1 GFR Category

CKD can be classified into five categories based on GFR values (Levin et al., 2013).

Table 1.1: GFR categories in CKD

GFR category	GFR (ml/min/1.73m^2)
G1	≥90
G2	60 – 89
G3a	45 – 59
G3b	30 – 44
G4	15 – 29
G5	<15

GFR may be determined using serum creatinine values and GFR estimation equation which may include Cockcroft-Gault, MDRD, and New Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. All of these equations are in common use but all may have some sort of bias therefore guidelines further recommend to use additional tests including cystatin C. (Michels et al., 2010)

1.2.2 Albuminuria Category

CKD can be classified into three categories based on urinary albumin values (Levin et al., 2013).

Table 1.2: Albuminuria categories in CKD

Category	Albumin Excretion Rate (AER) (mg/24 hr)	Albumin-to-creatinine ratio (ACR) (mg/g)
A1	<30	<30
A2	30 – 300	30 – 300
A3	>300	>300

1.3 Causes of CKD

The major causes of CKD includes diabetes mellitus, hypertension and glomerulonephritis, which makes up to two-thirds of the renal failure cases worldwide. Other less common causes may include polycystic kidney disease, malformations, lupus, recurrent urinary tract infections, lead poisoning, hemolytic-uremic syndrome, hepatitis B and C, and obstructions to urine flow due to problems like renal stones, tumors or an enlarged prostate gland in men (A. Levey et al., 2007; Webster et al., 2017).

1.4 Risk factors of CKD

There are a number of risk factor that can increase the likelihood of developing or complicating CKD which includes a family history of End Stage Renal Disease (ESRD), old age, low birth weight, African-American race, uncontrolled hypertension, prolonged hyperglycemia, cigarette smoking and obesity (Haroun et al., 2003; Kazancioğlu R., 2013).

1.5 Complications of CKD

Kidney failure is usually associated with multiple complications which include increase in all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anemia, mineral and bone disorders, and fractures. Worldwide, diabetes mellitus is the most common cause of CKD. The poor populations is at the high risk while screening and intervention can prevent CKD, and where management strategies have been implemented the incidence of end-stage kidney disease has been reduced (Thomas, Kanso, & Sedor, 2008; Bello et al., 2017).

1.6 Management of CKD

KDIGO has developed the most recent guidelines for diagnosis and management of CKD in 2012, these guidelines have been endorsed by NKF KDOQI, the prime body responsible for development of guidelines for the renal diseases. CKD is a complex disease which progress at fairly high speed and tends to damage the body organs and can cause many complications therefore its management is also focused on two different approaches i.e. prevention of progression of CKD and prevention of complications of CKD (Stevens & Levin, 2013; Cheung et al, 2021).

1.6.1 Prevention of progression of CKD

Large data of clinical trials have demonstrated that the progression of CKD can be delayed by controlling blood pressure and use of agents which block the Renin Angiotensin Aldosterone System (RAAS) of which the most commonly used are Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARB) (Cheung et al, 2021). Blood pressure targets should be set for individual patients based on their age in the light of recommendations of Joint National Commission (JNC) 8 guidelines (Abel et al., 2015).

1.6.1(a) Renin Angiotensin Aldosterone System (RAAS)

The antihypertensive therapy in the elderly patients with CKD should be tailored by considering age, comorbidities and other therapies, with gradual escalation of treatment and keeping a close eye on electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and adverse effects of the therapy. The guidelines further recommend that in adult CKD patients with urinary albumin excretion < 30mg/24 hours, both ACE inhibitors and ARBs are recommended for use in CKD to delay the progression of disease and kidney damage. Superiority of any one of them is not evident therefore

either one can be used based on patient and therapy related factors but usually 2 – 5 % patients on ACEIs experience persistent dry cough which may become a reason for selecting ARB instead of ACEI, otherwise both demonstrate similar efficacy and safety profile. (Levin et al., 2013).

Table 1.3: Choice of antihypertensive therapy based on urinary albumin levels in diabetic and non-diabetic patients

Type of patient	Urinary albumin	Actual Blood pressure	Target blood pressure	Choice of drug
Diabetic and non-diabetic	< 30mg / 24 hr	>140 / >90mmHg	≤140 / ≤90mmHg	ACE-I or ARBs
	> 30mg / 24 hr	>130 / >80mmHg	≤130 / ≤80mmHg	ACE-I or ARBs

The major actions of RAAS blockers include reduction in blood pressure through generalized arterial vasodilatation, reduction in urine albumin excretion and Reno-protection by vasodilation of afferent and efferent arterioles in the kidney resulting in decreased intra-glomerular pressure and hence reduction in GFR as well. Reduction in sodium-water retention and blood pressure by reduction in renal secretion of aldosterone. Other non-renal effects of RAAS blockers also include inhibition of fibrosis and enhancement of vascular and cardiac remodeling.

Immediately after the initiation of ACE-I/ARB's a 30% reduction in GFR (i.e. 30% increase in serum creatinine) is observed due to their physiologic effects, but more than 30% increase in serum creatinine may indicate renal artery stenosis. Therefore, in advanced stages of CKD, discontinuation of RAAS blockers including ACE-I or ARBs can allow a clinically significant increase in GFR and thus can help delay in development of end-stage renal failure (Santos, Krieger, & Pereira, 2012).

Since ACE-I or ARBs causes reduction in sodium-water retention by inhibiting the secretion of aldosterone therefore adding aldosterone antagonists along with any one of these drugs shows greater efficacy as compared to using it alone or with other antihypertensive drugs (Pisoni et al., 2012).

Both ACEI/ARBs can be used in CKD patients with cardiovascular comorbidities including heart failure, myocardial infarction, history of stroke, or high CV risk but keeping in view the major adverse effects like hyperkalemia and reduction in GFR. All ACE-I are extensively metabolized and their active metabolites are excreted through kidneys except Fosinopril and trandolapril which are 50% excreted through liver. The dose of ACEIs is titrated to achieve maximal clinical output regardless of its route of excretion. All ARBs are substantially excreted by liver and like ACE-I their dose is also titrated for maximal clinical output. If hyperkalemia occurs in a patient taking renally excreted ACE-I, the possible interventions may include dietary consultation to avoid potassium rich diet, reducing the dose, switching to non-renally excreted ACE-I like fosinopril or trandolapril, adding potassium losing diuretic (like thiazide and loop diuretics) and if dehydration occurs due to any underlying illness like vomiting, diarrhea or high fever occurs, reduce the dose or stop the use of ACE-I/ARBs (Sica & Gehr, 2002; Zhang et al., 2017).

1.6.2 Prevention of complications of CKD

There are many complications which can be developed after CKD but the major complications which needs active management includes acute kidney injury, glycemic control, anemia, metabolic bone disease and acidosis.

1.6.2(a) Acute kidney injury

Every CKD patient should be considered at high risk of developing Acute Kidney Injury (AKI). KDIGO guidelines recommends the management of AKI by using intravenous crystalloids for expansion of intravascular fluid in patients not at risk of having hemorrhagic shock along with management of hemodynamic and oxygenation parameters to control worsening of AKI symptoms. The use of vasopressors like norpinephrine is better as compared to dopamine in controlling the overall mortality rate, since recent controlled trials has demonstrated that dopamine administration does not confer clinically significant protection from renal dysfunction (Holmes and Walley, 2003). Stress induced hyperglycemia can lead to further complications therefore administering insulin therapy is also recommended to keep the blood glucose level in the range of 110 – 149 mg/dl. The use of aminoglycosides and diuretics should be avoided except in cases of severe volume overload (Kellum & Lameire, 2013).

1.6.2(b) Glycemic control

Diabetic nephropathy occurs in about 25–40% of diabetic patients within 20–25 years of disease onset and is an independent risk factor for early death due to cardiovascular disorders. The mortality rate in people with diabetes and urinary ACR >300 mg/g is more than twice that in those with normal urinary albumin levels (Kellum & Lameire, 2013).

The KDIGO guidelines recommend a target hemoglobin A1c (HbA1c) of 7.0% to prevent or delay the progression of diabetic kidney disease, a microvascular complication of diabetes. The target HbA1c should be extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. In people with CKD and diabetes, the glycemic control should be part of a multifactorial intervention strategy

which includes addressing blood pressure control and cardiovascular risk by promoting the use of angiotensin- converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically required (Andrassy, 2013).

1.6.2(c) Anemia

Anemia is an important complication of CKD because it contributes significantly to the heavy symptom burden of CKD. It has a major impact on the lives of people with CKD but it is potentially reversible with appropriate treatment. The KDIGO guidelines recommend diagnosing anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl in males and <12.0 g/dl in females.

Administering Iron therapy in CKD patients is very important for following reasons

- Reduce severity and symptoms of anemia
- Avoid blood transfusion
- Reducing dose of Erythropoietin Stimulating Agents (ESA) therapy
- Reducing hypo responsiveness to ESA therapy

IV Iron therapy is recommended for management of Anemia for following type of patients

- CKD patients with anemia not on iron therapy or ESA therapy in which increase in Hb value is desired and they have Ferritin <500ng/ml
- CKD patients with anemia on ESA therapy but not on iron therapy in which increase in Hb or reduction in ESA dose is required and they have Ferritin <500ng/ml

Iron therapy should ideally be stopped during systemic infection and is usually preferred than oral due to its compliance issues and gastrointestinal side effects. Oral iron therapy is started at 200mg iron daily (i.e. three tablets of ferrous sulfate 325mg each providing 65mg iron). It is better to administer small multiple doses of oral Iron. If the

clinical outcomes are not obtained after 1 – 3 months of therapy, then switch to Intravenous (IV) therapy. IV iron can be administered as one single large dose or repeated smaller doses. Usually IV iron is started with approximately 1000mg and then repeated based on the clinical effects (Lankhorst & Wish, 2010).

1.6.2(d) Mineral and bone disorders (MBD)

Changes in bone mineral metabolism and alterations in calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function declines. These changes are grouped under the umbrella term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) which includes renal osteodystrophy and extraskeletal (vascular) calcification related to abnormalities of bone mineral metabolism. Renal osteodystrophy is the component of CKD-MBD that is identified and quantified through bone biopsy histomorphometry and includes osteitis fibrosa (hyperparathyroidism), osteomalacia, and adynamic bone disease (Hou et al., 2018).

The KDIGO guidelines for management of CKD-MBD recommends the following treatment approaches

- Lowering serum phosphate levels by dietary restriction or administration of phosphate binders
- Maintaining the calcium levels to avoid hypocalcemia especially due to vitamin D deficiency since it can contribute to pathogenesis of secondary hyperparathyroidism and renal osteodystrophy.
- Managing abnormal parathyroid hormone levels through use of calcimimetics, calcitriol, or vitamin D analogues or their combination.

- Treatment with bisphosphonates, osteoporosis medications & growth hormone can be carried out keeping in view the individual risk and benefits since no evidence based data is available (Group, 2009a).

1.6.2(e) Acidosis

Metabolic acidosis is one of a common complication of CKD and its severity rises with the progression of CKD and reduction in GFR. Adaptations in acid excretion by the kidneys initially prevent a fall in serum bicarbonate concentration but as GFR continues to decline below 40 ml/min/1.73 m2, metabolic acidosis may develop. The KDIGO guidelines recommended that treatment with oral bicarbonates supplementation should be started in patients with serum bicarbonate concentrations <22 mmol/l to maintain serum bicarbonate within the normal range (Kraut & Madias, 2010).

The study of incidence, prevalence, risk factors and causes of CKD can help to control the disease burden and manage the financial resources in a more appropriate way along with improved patient care. Since Pakistan does not have their own clinical practice guidelines for CKD therefore a difference in treatment approach can exist among different nephrologists throughout the country. Due to high patient load, and limited number of nephrologists the routine CKD care is mostly provided by general practitioners which are not trained in CKD management (Saeed et al., 2020). Studying the disease outcomes with current practices, knowledge and practices of health care professionals regarding latest trends will help us identify the gaps where to work for enhanced therapeutic management. Study on the specific outcomes of patients with mineral bone disorders (MBD) will add high value to the already missing literature on this topic. A systematic study on MBD will help to suggest healthcare professionals and health authorities to undertake steps to enhance the health outcomes to reduce overall morbidity and improve patient quality of

life. The study of knowledge, attitude and practices will help to identify physician related issues and to overcome such issues by proposing changes in curriculum or training practices or continuing medical education.

1.7 Problem statement

- None of the published studies have determined the prevalence of osteoporosis among CKD patients in Pakistan.
- The clinical outcomes of the CKD patients in Pakistan are not yet studied.
- The clinical outcomes of the currently administered drug therapies for the osteoporotic conditions among CKD patients in Pakistan is unknown.
- The impact of patient related as well as drug related factors on the clinical outcomes of the CKD patients in Pakistan is not studied.
- There is need to have a validated tool to determine the knowledge, attitude and practices of the physicians towards CKD.
- The knowledge, attitude and practices of healthcare professionals towards CKD management in Pakistan is unknown.

1.8 General objectives

This study aims to determine the drug therapy, clinical outcomes, and factors affecting them in CKD patients with MBD in Pakistan. The study also aims to determine physician's Knowledge, Attitude and Practices (KAP) of CKD.

1.9 Specific Objectives

1. To study the prevalence of osteoporosis among CKD patients in Pakistan
2. To study the clinical outcomes and factors affecting drug therapy in CKD patients in Pakistan.

3. To study the management of osteoporosis in CKD patients along with the measure of the clinical outcomes and factors affecting the osteoporotic conditions.
4. To develop and validate a tool to determine KAP of physicians regarding CKD.
5. To determine KAP of physicians regarding CKD.
6. To determine pharmacist's knowledge regarding CKD.

1.10 Significance of Study

The study will determine the prevalence of osteoporosis which will help to realize the severity of the problem and can be a guidance for policy makers to set up priorities and define future goals. The study will help to raise the awareness regarding the importance of osteoporotic conditions as a significant risk factor among CKD patients. This study will be helpful to enhance the knowledge of physicians and pharmacist and improve attitude and practices towards osteoporotic conditions of the CKD patients. The study will help to reinforce the need to improve the knowledge and train the healthcare professionals to prepare them to manage the CKD patients as per best international practices. Dissemination of the findings of this study to the policy makers, health authorities and healthcare professionals will serve as feedback of the current practices and will serve as a turning point to improve the clinical practices to ensure better clinical outcomes among CKD patients.

1.11 Thesis Overview

Thesis overview is given in Figure 1.1

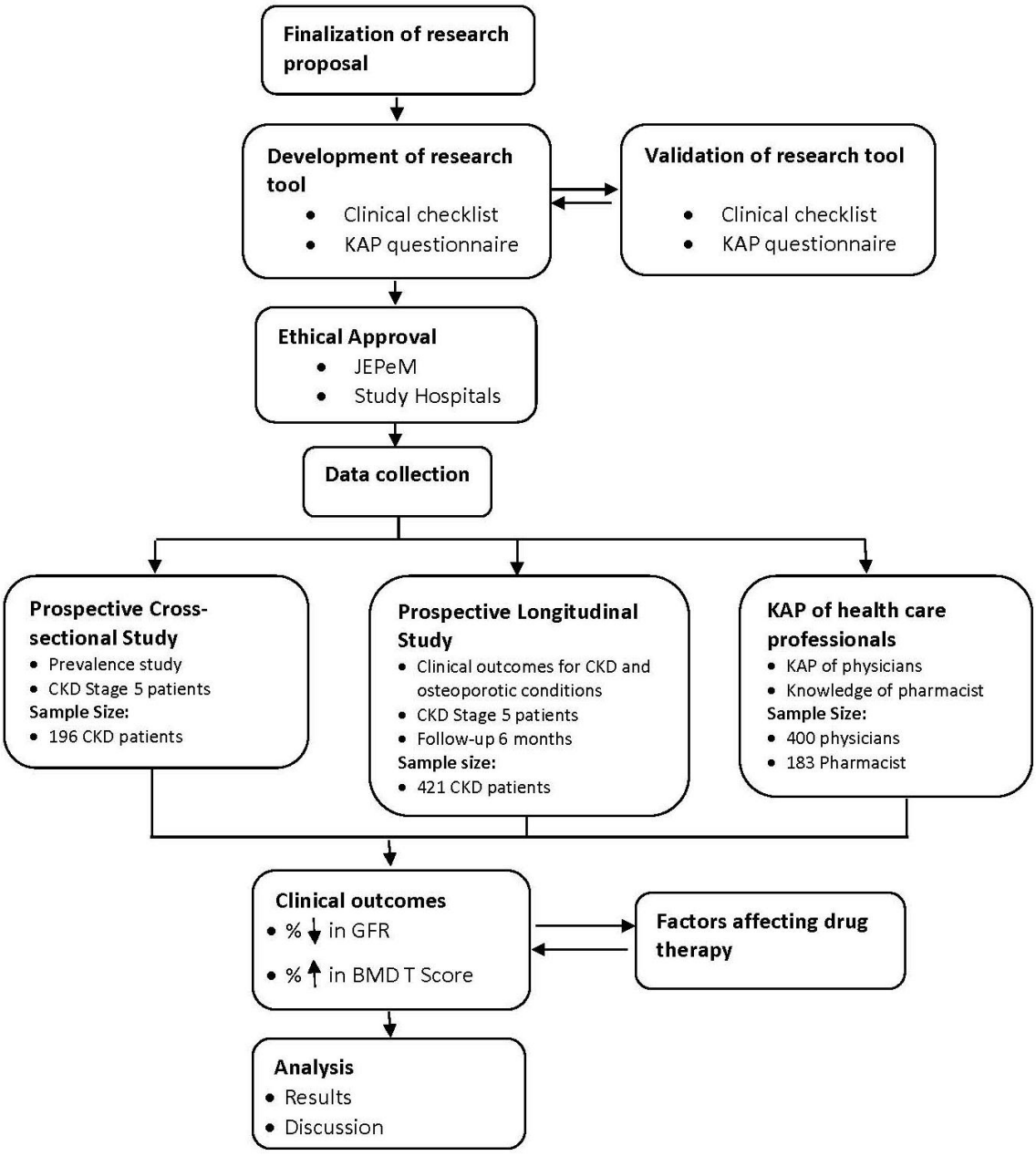

Figure 1.1: Thesis overview

CHAPTER 2
LITERATURE REVIEW

2.1 Prevalence of CKD

The reported annual incidence from developing countries varies from 34 to 240 per million population (K. Chugh, Jha, & Chugh, 1999), which is in contrast to an incidence between 98 and 198 per million population per year reported from end stage renal disease registries maintained in the developed countries (K. S. Chugh & Jha, 1995). The comparison is also evident from the graphical representation provided below (Kepler, 2010; A. S. Levey & Coresh, 2012).

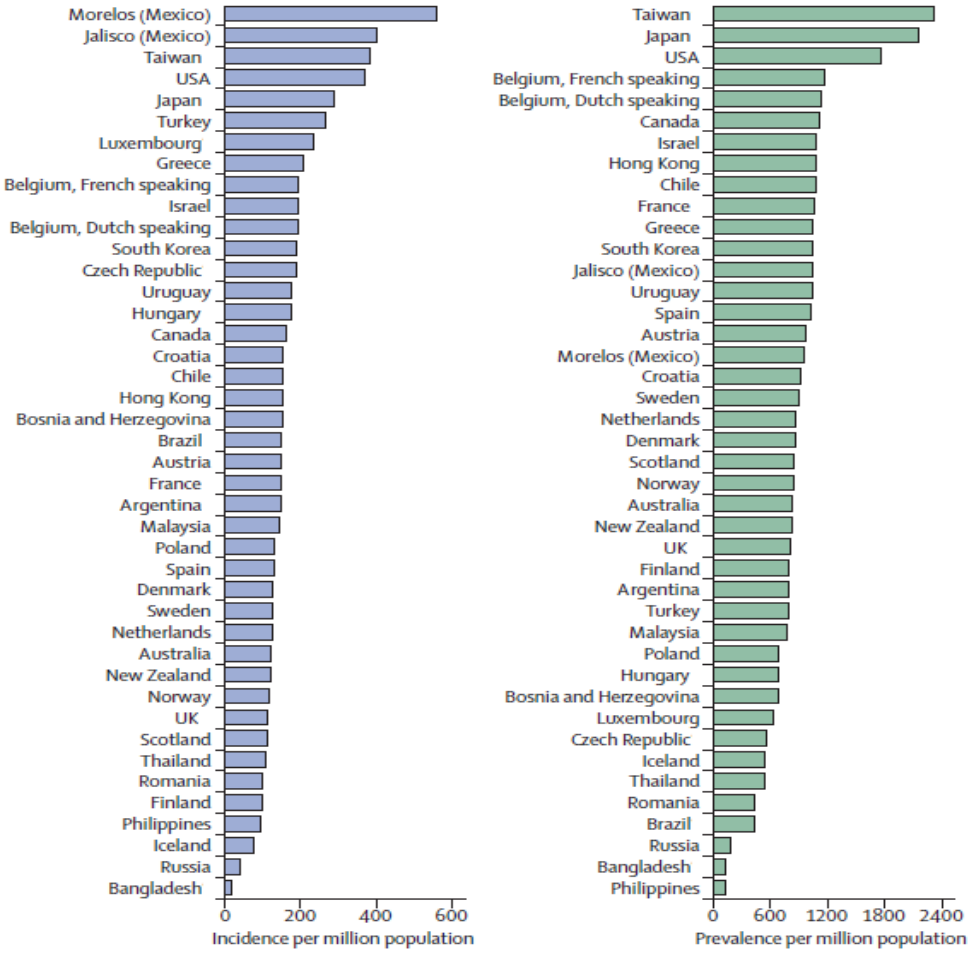

Figure 2.1: Incidence and prevalence of CKD

A study conducted in a French urban area on 2775 patients revealed that the annual incidence was twice as high in males than in females up to 75 years and three times as high in patients above 75 years age. (Jungers et al., 1996). Prevalence is estimated to be 8–16% worldwide. As per a systematic review, three out of these six studies reported higher prevalence of CKD among men ranged between 8.1% to 21.0%. However, rest three studies reported that the CKD prevalence was higher among female participants ranged between 16.3% and 19.1% than their male counterparts. Majority of the studies in South Asia reported higher prevalence of CKD among men, which is in contrast with the pattern of gender distribution of CKD across the globe. (Hasan et al., 2018).

Complications include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anemia, mineral and bone disorders, and fractures. Worldwide, diabetes mellitus is the most common cause of CKD. The poorest populations are at the highest risk (Jha et al., 2013). The global prevalence of CKD was estimated in two meta-analyses. Their results were remarkably similar, although both note major limitations and methodologic heterogeneity in the studies reviewed. A meta-analysis of 44 country prevalence studies estimated the worldwide prevalence of CKD at 13.4% (Hill et al., 2016). A meta-analysis of 33 prevalence studies estimated worldwide prevalence of CKD by sex at 10.4% in men and 11.8% in women (Mills et al., 2015).

2.1.1 Prevalence of CKD in Pakistan

The exact data regarding the prevalence of CKD in Pakistan is not available. The annual incidence of end-stage renal disease in Pakistan is estimated at about 100 per million populations according to a single center study. The annual transplant rate is about

300 which is less than 3 per million population. A total of 1,400 renal transplants have been performed from inception, two thirds of which are from living related donors (S. Rizvi & Naqvi, 1996). In one study based in Karachi in which in 12 representative communities were studied, the overall prevalence was determined to be 12.5% (Jessani, Bux, & Jafar, 2014). There is still very limited data available on the risk factors of renal diseases leading to CKD in Pakistan. Two center based studies from Karachi found chronic glomerulonephritis as the leading cause of ESRD in dialysis patients (S. Rizvi & Naqvi, 1996). A study conducted at Sindh institute of urology found diabetes mellitus as the most common known cause of CKD followed by hypertension (S. A. H. Rizvi & Manzoor, 2002).

Lack of a central registry makes epidemiological assessment extremely difficult and inadequate in Pakistan. Most of the data regarding disease burden estimates are mostly center based (Ullah, Butt, Masroor, Kanwal, & Kifayat, 2015). In another study conducted among 332 individuals the overall prevalence of reduced GFR was 29.9% in men and 32.5% in women (T. H. Jafar, Schmid, & Levey, 2005). In a study to find out the prevalence of CKD in district Mardan, samples were collected from 3000 patients and the prevalence of CKD patients was reported to be 8.2% in district Mardan. (Shams, Khan, Ayaz, & Afridi, 2018). Around 10 percent of patients with kidney failure receive any kind of renal-replacement therapy. Although the number of hemodialysis centers is increasing in many regions of Pakistan, most patients who begin to receive dialysis die or stop treatment within the first three months because of cost constraints. Kidney transplantation is the cheaper option, but only about 5 percent of patients with kidney failure receive a transplant (T. Jafar, Islam, & Poulter, 2006). The shortage of donors is a universal problem, and paid organ donation accounts for 70 percent of all transplantations in

Pakistan till 2010. After the organ transplant ordinance in 2010 in Pakistan, the per week number of transplant cases have been increased from 3 in pre-ordinance period to 10–12 cases per week post-ordinance (Rizvi et al., 2010). In Pakistan, the treatment of ESRD is a low priority for cash-strapped public hospitals, and in the absence of health insurance plans, or private insurance (Sakhuja & Sud, 2003). In Pakistan, around 10% of all patients receive any kind of renal replacement therapy due to economic constraints and lack of facilities. In Pakistan, only about 5% of all patients with end stage renal disease receive a kidney transplant (Sakhuja & Sud, 2003).

2.2 Mortality rate of CKD

The mortality rate due to CKD was studied by Centre for Disease Control (CDC), USA which was found to be 13.2 deaths per 100,000 standard population in 2014 which was increased by 1.5% in 2015 to 13.4 deaths per 100,000 population. This rate was further reduced by 2.2% in 2016 to 13.1 deaths per 100,000 population and did not significantly changed in 2017 (Kochanek, Murphy, Xu, & Arias, 2017; Murphy, Xu, Kochanek, & Arias, 2018; J. Xu, Murphy, Kochanek, & Arias, 2016). In another study on older adults having CKD, the mortality during follow-up was 19.6% for age 65–70 years, 33.4% for age 71–80 years, and 55.7% for age >80 years (Weiss et al., 2015). The mortality hazard ratio reported in a recent study across Europe was reported from 0.22 to 1.30 (Brück et al., 2018). In another study including 27, 998 patients with reduced GFR of less than 90 mL/min per 1.73 m^2 the mortality rate was 19.5% to 45.7% (Keith, Nichols, Gullion, Brown, & Smith, 2004). The exact mortality rate and prevalence of CKD in Asia is not yet known and therefore a protocol for a collaborative overview was developed and till date 7 countries including China, Japan, Korea, Taiwan, Thailand, Malaysia and India have participated in this collaborative project and till the completion of this overview exact

prevalence and mortality will be known for Asia region as well (Liyanage et al., 2017). The mortality rate of CKD is not studied in Pakistan and no data can be extracted from the web which involved study of mortality rate in CKD patients in Pakistan, this might be due to lack of a central registry (Imtiaz, Salman, Qureshi, Drohlia, & Ahmad, 2018).

2.3 Clinical outcomes of CKD

Clinical outcomes are measures of various factors / parameters that indicates a change in health, function or quality of life as a result of clinical care. There are various ways in which the clinical outcomes of CKD can be measured it includes changes in serum creatinine level, GFR values, urine to albumin ration, blood pressure, urine output, body weight, hemoglobin level, serum phosphate levels, serum calcium levels, serum potassium levels, serum urea levels, serum bicarbonate levels any some other biochemical markers depending on type of complications and disease stage (Yamashita, Yoshida, Ogawa, Tsuchiya, & Nitta, 2011). For determining risk of fracture Bone Mineral Density (BMD) Scan be used, which have been determined previously (West et al., 2015).

The clinical outcomes studied by Luo et al., were all-cause death and hospitalizations, and RAAS blocker discontinuation (Luo, Brunelli, Jensen, & Yang, 2016). CKD is a major health problem and is associated with increased risk for cardiovascular disease and end stage renal diseases. The prevalence of CKD is increasing rapidly in urbanizing country like Pakistan, where a significant population of 180 million is predisposed to diabetes and hypertension.

2.4 Factors affecting drug therapy in CKD

Acute renal failure is a complication in critically ill patients that has been associated with an excess risk of hospital mortality. Whether this reflects the severity of the disease or whether acute renal failure is an independent risk factor is unknown. One

study was aimed to analyze severity of illness and mortality in a group of critically ill patients with acute renal failure. Five interventions were associated with nonsurvival (mechanical ventilation, single vasoactive medication, multiple vasoactive medication, cardiopulmonary resuscitation, and treatment of complicated metabolic acidosis/alkalosis). The results of the study suggest that acute renal failure in patients undergoing renal replacement therapy presents an excess risk of in-hospital death (Metnitz et al., 2002). In another study conducted in Pakistan to assess the pattern and predictors of medication dosing errors in CKD patients in a tertiary care setting in Pakistan. It was observed that only 41.8% of prescribed drugs were properly adjusted. The predictors of medication dosing errors were the severe-to-end stages of CKD, the presence of a comorbidity such as hypertension, and a higher number of prescribed medicines (Saleem & Masood, 2016).

2.5 Osteoporotic conditions in CKD

KDIGO sponsored a conference in 2005 to define the bone related complications due to CKD. The recommendations from that conference were that

- the term "renal osteodystrophy" be used exclusively to define alterations in bone morphology that are associated with CKD and
- the term "chronic kidney disease–mineral and bone disorder" (CKD-MBD) can be used to describe the broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism as a result of CKD (Moe & Drüeke, 2008).

The KDIGO CKD-MBD guidelines 2017 have recommended to diagnose the patients on the following basis:

- Measurements of serum Parathyroid Hormone (PTH) or bone-specific Alkaline Phosphatase (ALP) to evaluate bone disease because markedly high or low values predict underlying bone turnover.
- Bone Mineral Density (BMD) testing to assess fracture risk if results will impact treatment decisions.
- Perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions

There have been many studies based on impact of different treatments on CKD-MBD. Most of studies are based on phosphate lowering therapies. Most placebo or usual care controlled studies were among participants with CKD G2 to G5 not requiring dialysis, while most head to head studies involved participants with CKD G5 treated with dialysis. In CKD G2 to G5, compared with placebo or usual care, sevelamer, lanthanum, iron and calcium-based phosphate binders had uncertain or inestimable effects on death (all causes), cardiovascular death, myocardial infarction, stroke, fracture, or coronary artery calcification. There were no head-to-head studies of iron-based binders compared with calcium. It is uncertain whether the effects of binders on clinically-relevant outcomes were different for patients who were and were not treated with dialysis in subgroup analyses. In studies of adults with CKD G5D treated with dialysis, sevelamer may lower death compared to calcium-based binders and incur less treatment-related hypercalcaemia, while we found no clinically important benefits of any phosphate binder on cardiovascular death, myocardial infarction, stroke, fracture or coronary artery calcification (Ruospo et al., 2018). To determine the spectrum of CKD- MBD in the Pakistani population, a retrospective review of the medical records of 63 native Pakistani CKD stage-5 patients

was performed. The study concluded that at initiation of hemodialysis, a significant number of patients had low PTH and a similar percentage of high PTH in our population states. Therefore, the study recommends early assessment of renal bone disease spectrum to prevent morbidity and mortality associated with mineral bone disorder in CKD patients (Hafeez et al., 2015). To review the benefits and harms of osteoporosis medications compared with placebo, usual care, or active control in terms of BMD, fractures, and safety in patients with CKD, a meta-analysis was conducted. The study concluded that effects of osteoporosis medications on BMD, fracture risk, and safety among patients with CKD are not clearly established (Wilson et al., 2017). In another study it was concluded that that the prevalence of renal osteodystrophy was significantly increased. Secondary hyperparathyroidism (Osteitis Fibrosa Cystica) is the most common pattern followed by mixed osteodystrophy and adynamic bone disease among CKD patients (Jat, Mal, & Kumar, 2016). In a multinational study involving patients from Middle East, South Asia, Eurasia, and Africa, 2250 CKD patients were studied for management of their mineral and bone disorders and it was concluded that the current practices for the management of bone and mineral metabolism in CKD patients in the study region fall far short of meeting the KDIGO target range which includes the recommended ranges for serum calcium (≥8.5–≤9.5 mg/dL), phosphorous (≥2.5–≤4.5 mg/dL) and PTH (≥ lower limit of normal and ≤ upper limit of normal) (Shaheen et al., 2016). Most of the available literature suggest improving outcomes in CKD patients with MBD. No systematic study is conducted in Pakistan which involves patients from multiple centers, there is a dire need to conduct such studies to determine outcomes as well as factors affecting the outcomes based on current treatment practices.

2.6 Knowledge, attitude and practices of CKD

No systematic study has been conducted on physicians with adequate sample size using a reliable tool. In a study aimed to assess the knowledge of physicians on CKD and their attitudes regarding referral it was observed that only 58.8 % of doctors identified the correct definition of CKD and general practitioners and non-nephrology specialists lack general knowledge on CKD (Choukem et al., 2016). In another study only 11.7% physicians correctly identified CKD as occurring in approximately one in every ten individuals. The knowledge regarding CKD screening was found to be adequate, however a gap between CKD screening knowledge and the prescribing practices of the physicians was identified (Agaba et al., 2011). In another study only 35% physicians had adequate CKD knowledge with overall knowledge reducing with each 10 years increase in age (Israni, Shea, Joffe, & Feldman, 2009). In a study to determine knowledge of practitioners regarding CKD concluded that there is a need for continuing education and awareness among physicians regarding CKD management since it may have a significant impact on CKD management and outcome (Tamizuddin & Ahmed, 2010). In another study it was determined that there was a paucity of knowledge regarding CKD management guidelines and staging of CKD. The majority physicians do not read medical journals to keep their knowledge up-to-date while junior doctors scored better than attending doctors in the knowledge and practice parameters (Mahmud, Hussain, Kamal, Samoo, & Khan, 2016)

2.7 Systematic review of prevalence of osteopenia & osteoporosis among CKD Patients

In order to provide an updated summary on the prevalence of low bone mass (i.e., osteopenia and osteoporosis) among the CKD patients, we undertook an updated systematic review to access the prevalence of osteopenia and osteoporosis among CKD

patients from different stages and to identify the factors associated with difference in the prevalence. This systematic review gathers the evidence of prevalence through the measure of BMD performed through DXA screening along with other biochemical or radiological assessments. It is generally known that impaired kidney function can lead to low bone mass and developing osteoporosis, becoming a risk factor for fracture but the most of the research is only focused on CKD G5 patients on dialysis. The patterns and impact of low bone mass in patients with moderate to severe kidney failure are less studied. There is a variation in reported prevalence of osteoporosis and type of fractures among CKD patients of various stages. This review is aimed to study the prevalence of low bone mass including osteopenia and osteoporosis among CKD patients from stage G3a to stage G5.

2.7.1 Data sources

Studies were identified through a comprehensive literature search of databases including Scopus, PubMed, Medline, Science Direct and Google Scholar, and additional sources including Cochrane Library from the inception of these sources until August 2019. The reference lists of the selected research publications were also analyzed and reviewed to make sure no relevant article have been missed from our initial search.

2.7.2 Search strategy

The keywords used for searching relevant articles were “prevalence,” “osteopenia,” “osteoporosis,” “Chronic Kidney Disease,” “CKD patients,” “Chronic Renal Failure,” “CRF patients,” “Bone Mineral Density,” and “low bone mass.” Boolean operators such as ‘AND’ and ‘OR’ were used to increase the sensitivity and specificity of the search when needed.

2.7.3 Inclusion and exclusion criteria

Studies, in which osteoporosis / osteopenia was not determined using measure of BMD through DXA, were not included in the final review. Osteoporosis was defined according to WHO criteria, as a BMD T-score below 2.5 and osteopenia was defined as a T-score between –1.0 and –2.5. The articles identified were then screened based on the inclusion and exclusion criteria presented in Table 2.1.

Table 2.1: Criteria for inclusion and exclusion of studies in the review

Population	CKD patients' stage G3 to G5
Phenomenon of interest	The phenomenon of interest included • Measure of bone mineral density in CKD patients • Prevalence of osteopenia and osteoporosis among CKD patients
Primary outcome measure	The outcome measures of interest included but were not restricted to the following: • Method used for studying prevalence of osteoporosis in CKD patients • Impact of CKD stage and other factors on BMD levels • Difference in T score values for different sites among CKD patients
Types of studies	Quantitative cross-sectional / longitudinal clinical studies. Studies were included if they reported one or more of the outcomes detailed above
Exclusions	Following were excluded • Studies involving renal transplant patients • Studies not measuring bone mineral density • Studies not reporting the T score for BMD test • Studies not measuring both osteopenia and osteoporosis • Studies not following WHO criteria for osteoporosis using BMD T score values. • Studies including CKD patients having GFR values >60ml/min • Studies involving patient receiving medication known to influence bone and mineral metabolism such as corticosteroids, immunosuppressant, hormone replacement therapy, anticoagulants, lithium and anticonvulsants etc. • Studies involving patients below 18 years of age