Original Article

A Prospective Observational Study on Pattern of Drug Use and Burden of Polypharmacy in Patients with Chronic Kidney Disease in A Tertiary Hospital

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ABSTRACT

Background: Chronic kidney disease (CKD) represents a global public health burden with increasing prevalence worldwide. Suitable drug selection for patients with CKD is vital to avoid undesirable drug effects and to ensure optimum patient outcomes. Prescription pattern studies provide us the information regarding extent and profile of drug use, trends, standard treatment guidelines and overall, facilitates the rational use of drugs in a population. This study was undertaken, as despite the recognized challenging circumstances of pharmacotherapy in CKD patients, there are only few studies reported in the Indian literature about prevailing pattern of prescribing drugs, the burden of polypharmacy and predisposing factors in CKD, requiring more systematic studies.

Objective: To assess the prescribing pattern for chronic kidney disease (CKD), to find out the burden of polypharmacy & to assess comorbidities in CKD.

Methodology: 75 consecutive subjects of either gender aged >18yrs attending Department of Nephrology on outpatient and inpatient basis were recruited to the present study. Subjects diagnosed as per KDIGO classification to have chronic kidney disease by treating Nephrologist at Kempegowda Institute of Medical Sciences Hospital, Bangalore, were included and assessed for current therapy for CKD, comorbid conditions including type, duration, number of comorbidities and number of drugs / drug combinations used.

Results: The mean age group of study subjects was 55.12±13.4 years, with male preponderance. Majority of subjects were on 6 medications per day and most common comorbidity was hypertension.

Conclusion: The most common comorbidity was hypertension followed by diabetes and majority of subjects were suffering with CKD stage 4 and most prescribed CKD medication was N-Acetylcysteine + Taurine, antihypertensives were calcium channel blockers, antidiabetics were Soluble Insulin/ Insulin Isophane 30/70 and Tenligliptin, IHD medication was Aspirin + Atorvastatin and for anemia Darbepoetin.

Keywords: CKD; KDIGO (Kidney, Disease Improving Global Outcome) staging; Polypharmacy; Comorbidities; Calcium channel blockers.

INTRODUCTION

Chronic kidney disease (CKD) is characterized by a decrease in the glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for three or more months and abnormality in the kidney structure or its function.[1] It is mainly estimated based on decrease in the number of nephrons. It is more prevalent in the elderly population; studies have estimate that 23–36% of people ≥ 64 years of age have CKD.[2] However, while younger patients with CKD typically experience progressive loss of kidney function, 30% of patients over 65 years of age with CKD have stable disease. According to the World Health Organization (WHO), CKD contributes to nearly 8,50,000 deaths worldwide annually.[3,4] In India, the prevalence of CKD is 17.2% and it was more in males than females.[1,5] The rise in the number of CKD patients and consequent end-stage renal disease necessitating renal replacement therapy has placed a significant strain on health care.[5] Diabetes and hypertension have been reported to be the most common risk factors for CKD[6,7], other risk factors are damage to kidney function, recurring kidney infections, inflammation, congenital kidney disease, obstruction of urinary tract, autoimmune disorders, smoking, obesity, and coronary artery disease.[1] Patients with CKD suffer from a high number of comorbidities, including underlying diseases and consequences of impaired kidney function, such as hypertension, diabetes, cardiovascular disease (CVD), CKD-related bone and mineral disease and anemia.[2] Because of the chronic nature of the disease and presence of co-morbidities, CKD patients need multiple drug therapy with complex medication regime, increasing cost of the therapy, the adverse effects, drug interactions, which poses a challenge for the treatment of CKD patients.[1,8] Rational drug prescription is difficult in CKD patients due to a higher risk of drug-related problems since they need complex therapeutic regimens requiring frequent monitoring and dosage adjustments. Management of CKD patients involve multifaceted and comprehensive treatment, which includes lifestyle/dietary modification, fluid management, multiple medications and as if it progresses, may require renal dialysis and renal replacement therapy. Drug utilization in CKD changes with time, physician, disease conditions and

population, which makes it important to study the drug utilization continuously over a period, on a regular basis. Despite the recognized challenging circumstances of pharmacotherapy in CKD patients, there are only few studies reported in the Indian literature about prevailing pattern of prescribing drugs, the burden of polypharmacy and predisposing factors in CKD, requiring more systematic studies and hence this study was taken up.

MATERIALS AND METHODS

This prospective observational study was done to assess the pattern of drug use and burden of polypharmacy in patients with chronic kidney disease. Following IEC approval **(KIMS/IEC/D002/M/2021)** and clearance, 75 consecutive subjects of either gender aged >18yrs diagnosed as per KDIGO classification guidelines to have CKD were included into the study. After confirming the diagnosis by treating Nephrologist, participants were enrolled by convenient/purposive sampling method from Jan 2021-June2022 (1.5 years). After obtaining written informed consent from all the research participants, complete procedure was explained in-detail. Participants satisfying following inclusion criterions were enrolled into the research. Study subjects of either gender aged >18yrs diagnosed as per KDIGO classification guidelines to have chronic kidney disease (irrespective of the cause for CKD). CKD subjects with single or multiple comorbidities, subjects with any acute infection/s like upper/lower respiratory trat infection, UTI etc, CKD subjects on immunotherapy, subjects with grade III, IV and V CKD not on dialysis and subjects willing to give written informed consent. Participants who did not fulfill inclusion criteria and with below conditions were excluded from the study. Subjects with grade I and II CKD, subjects with end stage renal disease (renal dialysis), subjects with surgical conditions like renal stone, tumors of genitourinary system, subjects with terminal illnesses due to malignancy, subjects planned for or post-renal transplant, subjects with chronic infections like tuberculosis, leprosy, HIV, HBsAg or HCV status, Pregnant and lactating women. Patient information regarding demographics, socioeconomic, present, past medical/ surgical, lifestyle (smoking, alcohol consumption) and family history were documented in the CRF (Case record form, which was designed by the study investigator to collect all the essential data) The details of the current therapy for CKD including the number of drugs/ drug combinations used, the therapeutic class, the route of administration, the dose, the frequency, and duration of administration was collected from patients by OPD records, prescriptions and through one to patient interview. Also, data was analyzed to obtain relevant information about the comorbid conditions including type, duration and number of comorbidities and number of drugs/ drug combinations used for different comorbidities. CKD progression, any change in the medication, biochemical parameters (blood urea and serum creatinine) and number of comorbidities were assessed at the baseline and at monthly intervals for 3 months. Biochemical parameters were recorded from the latest laboratory investigation reports documented in the clinical records. Concealment and professional secrecy were maintained for all the research participants. The data collected was entered into Microsoft Excel data sheet and was analyzed using SPSS software 19.0 version. The data collected was analyzed statistically using certain descriptive statistics namely mean, proportion, standard deviation, percentages. Results were also depicted in the form of percentages and graphs.

RESULTS

Table 1: Age & Gender Distribution (n=75)

Age (years)	Male n (%)	Female n (%)	Total n (%)
18-30	0	2	2
31-60	27	16	43
>60	19	11	30
Total	46	29	75
Mean ± SD	55.06±12.47	56.13±13.93	55.12±13.41

Table 2: CKD staging/grading OF CKD (n=75)

Staging/ Grading of CKD	n (%)
Stage 3	30 (40%)
Stage 4	36 (48%)
Stage 5	9 (12%)
Total	**75(100)**

*Majority of the subjects (48%) had stage-4 CKD

Table 3: Prescribed medications/ongoing therapy for CKD

Medications	n (%)
CKD Medications	
N-Acetylcysteine +Taurine	74 (98.6)
Pre & Probiotic	38 (50.6)
Prednisolone	17 (22.6)
Cyclophosphamide	1 (1.3)
Mycophenolate mofetil	4 (5.3)
Furosemide	24 (32)
Torsemide	7 (9.3)
Furosemide + Spirinolactone	1 (1.3)

Figure 1: Duration of CKD

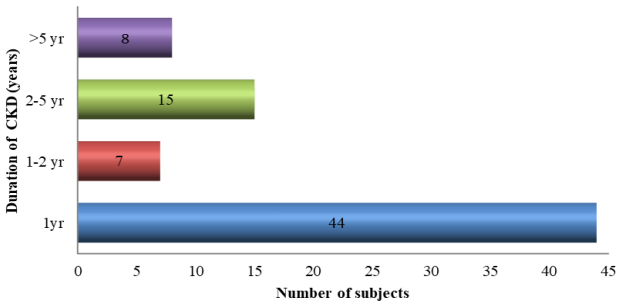

Table 4: Ongoing therapy- most common single and fixed combinations used for comorbidities (n=75)

Medications	n (%)
Antihypertensives	
Single Drug →Amlodipine	25 (33.3)
Fixed Dose Combination → Telmisartan + Hydrochlorothiazide	2 (2.6)
Antidiabetic Drugs	
Single Drug → Tenligliptin & Soluble insulin/Insulin isophane -30/70	16 (22.2)
Fixed Dose Combination → Glimipiride +Metformin	5 (6.6)
Drugs in IHD	
Single Drug →Aspirin	2 (2.6)
Fixed Dose Combination → Aspirin + Atorvastatin	12(16)
Drugs in anemia	
Single Drug → Darbapoietin	12 (16)
Fixed Dose Combination	-

Figure 2: Comorbidities (n=75)

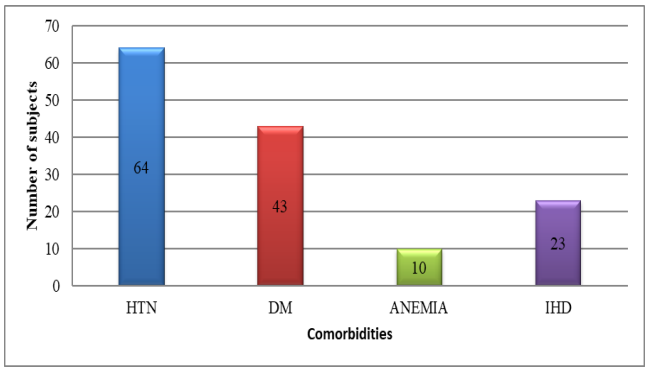

Figure 3: Number of medications per subject (n=75)

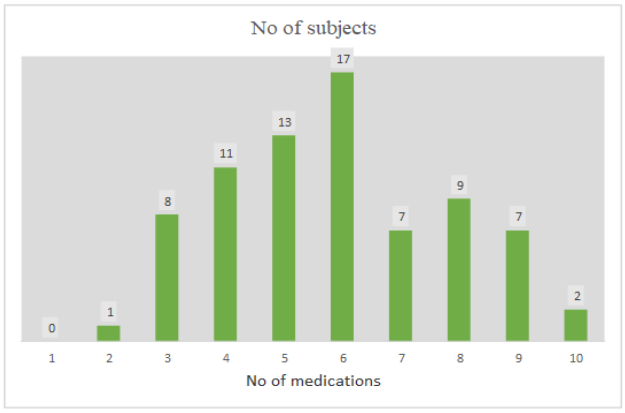

Table 1 shows the **demographic details** of study participants. Majority of the subjects (57.3%) were in the age group between 31-60 years and the mean age of population was **55.12±13.41** years. The mean age for males was 55.06±12.47 years and for females 56.13±13.93 years. **Duration of CKD** in the study subjects is summarized in the **Figure 1.** Out of the total 75 patients, majority of the subjects (58.6%) had onset of CKD within 1 year, 7% of the subjects had CKD history from 1- 2 years, 21.3% of the subjects from 2-5years and 10.6% of subjects suffering from CKD for more than 5years. **Table 2 summarizes CKD staging/grading of CKD** - Majority of subjects (48%) had CKD stage 4, 40% stage 3 and only 12% were suffering from stage 5 CKD. Co morbidities in the study subjects is summarized in the **Figure 2.** For Majority of subjects (85.3%), hypertension was the most common co-morbidity. Other comorbidities present were diabetes mellitus in 57.3%, anemia in 30.6% and IHD in 13.3% of study subject. The prescription pattern of CKD medications is summarized in **Table 3.** 98.6% of subjects received N-Acetylcysteine + Taurine, 50.6% received Pre & Probiotics, 22.6% received Prednisolone, 1.3% received Cyclophosphamide, 5.3% received Mycophenolate mofetil, 32% received Furosemide, 9.3% received Torsemide, 1.3% received Furosemide + Spironolactone. **Table 4** summarizes most common single and FDC prescribed for CKD and other comorbidities. Most common drugs prescribed as single drug for HTN was Amlodipine and FDC was Telmisartan + Hydrochlorthiazide. Most common drugs prescribed as single drug for Diabetes Mellitus was Tenligliptin and Soluble insulin / Insulin Isophane -30/70 and FDC was Glimiperide + Metformin. Most common drugs prescribed as single drug for IHD as single drug was Aspirin and FDC was Aspirin + Atorvastatin. Most common drugs prescribed as single drug for Anemia was Darbepoetin. **Figure 3** summarizes number of medications per subject. Among total 75 study subjects, 22.6% were on 6 medications, 17.3% on 5 medications, 14.6% on 4 medications, 12% on 8 medications, 10.66 % on 3 medications, 9.3% on 9 medications, 9.3% on 7 medications, 2.6% on 10 medications and 1.3% subjects on 2 medications.

DISCUSSION

In the present study, pattern of drug use and burden of polypharmacy in patients with chronic kidney disease were assessed in 75 consecutive subjects who attended the nephrology outpatient department at KIMS Hospital and Research center, a tertiary care teaching hospital.

The mean age was **55.12 ± 13.41years**. Among total 75 subjects, majority of the subjects (57.3%) were in the age group between 31-60 years and this result is consistent with study conducted by Avez Ali,[9] the mean age of population was **58.28 ±13.12** years with majority of them were in the aged group of >60years. In other study conducted by Deepak Jain[5] the mean age of the patients was 48.02 ±15.40 years with majority of them were in the age below 50 years. The mean age for males was 55.06±12.47 years and for females 56.13±13.93 years. 62.6% of the subjects were male and 37.3% were female. The male predominance is probably because of the better awareness about health and economic independence compared to females. This result was similar with the study done by Hiroshi Kimura and etal[10] which showed male preponderance of 56%. The stage of CKD in the study subjects was categorized as per kidney disease improving global outcome (KIDGO) classification. Majority of subjects (48%) had CKD stage 4, 40% stage 3 and

only 12% were suffering from stage 5. This was similar to study conducted by Hilda O Hounkpatin and etal [11] were 41% were suffering from CKD stage 4, 38% with stage 3, 21% with stage 5 CKD. In study conducted by S. Rakshana and Preetha Selva[12] have shown that majority of subjects (84.83%) had CKD stage 5, 6.03% stage 4 and 5.14% had CKD stage 3. In other study conducted by Sowmya Santra[4] showed that majority (28%) had CKD stage 3, 20% stage 4, 26% had CKD stage 5. KIDGO is a global organization developing and implementing evidence-based clinical practice guidelines in kidney disease. It is an independent, volunteer-led, self-managed foundation incorporated in Belgium and accountable to the public and the patients it serves. Among Co morbidities, hypertension was the most common co-morbidity, followed by diabetes mellitus, anemia and IHD. Almost all the patients had more than one comorbidity. Study conducted by Latha Kamath and tal[3] shown hypertension was commonest comorbidity in 40% of the subjects. In other study done by Sourav Chakraborty and etal[7] shown anemia to be the most common comorbidity in 89% of the subjects followed by Hypertension in 85% of the subjects. In study conducted by Minyuan Ye etal[13] showed that use of N-Acetylcysteine reduces cardiovascular events among people with CKD. In study conducted by Na Tian etal[14] showed probiotic administration had potential benefit in improving symptoms and quality of life, reducing inflammation, and delaying the progression of kidney failure. In study conducted by Purna Atray etal[15] showed 5.54% received steroid, 10.13% received immunosuppressants. In study conducted by Rajesh Hadia etal[16] showed 23.02% received loop diuretics. N-Acetylcysteine (NAC) has been reported to protect the kidney from injury induced by contrast media, ischemia, and toxins. Its efficacy is controversial because of heterogeneity in study results and because of evidence that NAC can alter serum creatinine levels without affecting glomerular filtration rate. This confounding effect of N-acetylcysteine on serum creatinine has not been rigorously tested.[17] Rationale of using prebiotics and probiotics in CKD - Patients with CKD and end-stage renal disease (ESRD) present quantitative and qualitative alterations in the gut microbiota such as increased concentration of urea and ammonia in the bowel, compromised integrity of the intestinal barrier, and increased levels of inflammation. Probiotics include a vast array of products with living microorganisms whose purpose is to improve intestinal microbial balance and produce beneficial effects on one's health. The effects arising from the use of probiotics by patients with CKD are unclear, and only few studies have been carried out in this area.[18] Rationale of using Prednisolone, Cyclophosphamide and Mycophenolate mofetil in CKD subjects - Study conducted on CKD subjects with steroids and Immunosuppressive treatment (CS and IT therapy) by Li Tan etal[19] has shown that, combination may improve short-term renal outcome than steroid alone. Study conducted by Zhang etal[20] has shown that, Immunosuppressive therapy can significantly reduce proteinuria and ESRD risk in patients with IgAN, but with a concomitant increase in adverse reactions. Therefore, care is required in the application of immunosuppressive agents in IgAN. The principal use of diuretics in CKD is to reduce blood pressure and treat swelling (oedema). Diuretics facilitate the action of angiotensin-converting enzyme inhibitors (ACEIs) and other antihypertensive drugs to reduce the risk of coronary vascular disease among people with CKD. Diuretics can also help to control potassium levels in people with elevated potassium levels (hyperkalemia). Long-acting diuretics administered with antihypertensive drugs have been shown to increase patients' compliance with drug therapy. **There is a guideline called NKF KDOQI GUIDELINES for administration diuretics for CKD patients.** (https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/guide_12.htm). In our study poly pharmacy was observed in 73.1% of the study subjects and mean was **6±2.73**. A similar study conducted by IM Schmidt et al,[2] showed the prevalence of polypharmacy was high. At baseline, almost 80% of patients received polypharmacy and 20% were prescribed >10 different medications per day. The most common definition of polypharmacy is the concurrent use of ≥5 or ≥6 drugs. Patients with chronic kidney disease (CKD) often suffer from multiple comorbidities; therefore, polypharmacy is inevitable and highly prevalent.

Strength: This study may help in designing an effective therapeutic regime to treat CKD patients with comorbidities and educate the patients about change in lifestyle and adherence to drugs to prevent progression of disease. **Limitations**- Long term randomized controlled research may necessitate with the adequate number of follow-ups to achieve and to measure the accurate response for CKD medications, so more long-term studies are required.

CONCLUSION

The most prescribed CKD medication was N-Acetylcysteine + Taurine, among antihypertensives calcium channel blockers, among antidiabetics Soluble Insulin/ Insulin Isophane 30/70 and Tenligliptin, were mostly commonly used medications. Most common comorbidity was hypertension (64 (85.3%)) and majority of subjects were suffering with CKD stage 4. 22.6% were on 6 medications per day**.** Chronic kidney disease is a major public health issue worldwide and is associated with high morbidity and mortality. Developing countries like India, with its huge diabetic and hypertensive population, is becoming a major reservoir of CKD. Hence, appropriate drug selection for patients with CKD is important to avoid unwanted drug effects and to ensure optimal patient outcomes. In this regard, Prescription pattern studies are helpful to facilitate the rational use of drugs in a population.

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