A study on the pharmacological management of mineral bone disease in chronickidney diseasepatients inatertiary care hospital

Syed Irfan Ali Ahmed (Pharm.D)
Department of Pharmacy, Krishna Teja Pharmacy College, Tirupati.
irfanahamed7@gmail.com
Ph. No:7416436954

S.P.SrinivasNayak (Pharm.D)
Department of Pharmacy, Krishna Teja Pharmacy College, Tirupati.
spnayak843@gmail.com
Ph. No:9948434976

K.R.Madhuri (Pharm.D)
Department of Pharmacy, Krishna Teja Pharmacy College, Tirupati.
madhurikr19@gmail.com
Ph. No: 8919177372

Dr. B.Jyothi, Assistant Professor,
Department of Pharmacology, Krishna Teja Pharmacy College, Tirupati.
Jyothi_811@yahoo.co.in
Ph. No:9908324282

Dr. K.Umamaheshwar Rao, Professor and Head,
Department of Pharmacology
Sri Venkateswara Institute of medical Sciences, Tirupati.
Kavetimahesh40@gmail.com
Ph. No: 9849832292

Dr. V.Kiranmayi*, Assistant professor,
Department of Biochemistry
Sri Venkateswara Institute of medical Sciences, Tirupati.
kvinapamula@yahoo.co.in
Ph. No:9030956088

Dr. V.Siva Kumar, Senior Professor,
Department of Nephrology
Sri Venkateswara Institute of medical Sciences, Tirupati.
sa_vskumar@yahoo.com
Ph. No:9493547712

Abstract

Background: In patients with chronic kidney disease (CKD), along with progression of CKD, abnormalities of mineral and bone metabolism develop, which result in altered serum levels of minerals such as calcium and phosphorus, as well as abnormalities in parathyroid hormone (PTH) or vitamin D metabolism. Chronic Kidney Disease-Mineral Bone Disease (CKD-MBD) is a serious burden because of increased cardiovascular mortality thus making therapeutic improvements essential in CKD-MBD. The present study was aimed at evaluation of pharmacological management of CKD-MBD.

Methods:A retrospective study including 180 patients divided into two groups of 90 each (diabetes mellitus and non-Diabetes) was performed in the Department of Nephrology, SVIMS, Tirupati. Patients who were on follow up for at least 3 years (2015-2017) were considered, serum parameters were

measured at every six months with a total of 6 visits. First visit was taken as baseline and sixth visit as conclusion.

Results:The disease incidence of CKD-MBD is more common in male patients i.e. 67.8%. Serum calcium levels were significantly increased and eGFR was significantly decreased in all patients with CKD at conclusion compared to baseline.Further, Serum calcium levels were significantly increased at conclusion in CKD patients without DM and eGFR was significantly decreased at conclusion compared to baseline in CKD patients with DM. The proportion of untreated patients is high for all the drugs except vitamin D analogues in both subgroups of CKD patients.

Conclusion:Pharmacological intervention in CKD patients helps in the effective management of mineral bone disease by maintaining serum calcium, phosphate and calcium phosphorous product status.

Key words:calcium; calcium x phosphate; chronic kidney disease; mineral bone disease;phosphate

INTRODUCTION

ChronicKidney Disease(CKD)isanimportantglobalpublichealthproblem [1]. In India, theprevalenceofCKDstages1,2,3,4and5is reported to be7%,4.3%,4.3%,0.8%and 0.8%,respectively [2].Diabetes mellitus (DM), hypertension, autoimmunediseases,polycystickidney disease, systemicinfections,urinary tract infections, urinarystones, lower urinarytract obstructions, and drug toxicityare allconsideredinitiationfactors whichareconditionsthatdirectly resultinkidney damage,andare modifiable by pharmacologictherapy. Among these, DM,hypertension,andglomerulardiseasesare thethreemostcommoncausesof CKD [3]. Kidney playsanimportantroleinmaintaining calciumandphosphorus homeostasisalongwithparathyroidgland(PTG),intestines andbone [4]. Decreasing renal function results in progressivedeteriorationofmineral homeostasis,withadisruptionofnormalserumandtissueconcentrationsofphosphorus andcalcium,as well aschangesinthe circulating levelsofhormones includingparathyroid hormone (PTH),25-hydroxyvitaminD(25(OH)D),1,25-dihydroxyvitaminD(1,25$(OH)_2$D) or calcitriol,andother vitaminDmetabolites,fibroblast growth factor-23 (FGF-23)andgrowthhormone.Beginning inthe stage3 of CKD,the ability ofthekidneystoappropriatelyexcreteaphosphateloadisdiminished,leadingto hyperphosphatemia,elevated PTH,and decreased1,25$(OH)_2$Dwith associated elevations in the levelsofFGF-23 [5].

ChronicKidney Disease-MineralBoneDisease(CKD-MBD)isasystemic disorderofmineralandbone metabolismthat occurs duetoCKDand is manifestedby eitheroneora combinationof a) abnormalitiesofcalcium,phosphorus,PTH,orvitaminDmetabolism, b) abnormalitiesinbone turnover,mineralization,volume, lineargrowth, or strength and c) vascularorothersoft-tissuecalcification [6].

The reduced phosphate excretion which occurs due toimpairedrenalfunctionleads toretention of phosphate.Asa resultof that, thereis increasedsecretionofFGF-23onone handand impairedsynthesisofcalcitriolon the other.Decreased synthesisofcalcitriolis theresultofreducedrenalmass,phosphateretentionandtheeffectof increasedFGF-23 level.A low levelofcalcitriol together withretentionof phosphate leads tohypocalcaemia. These ultimately result in increasedsynthesisandsecretionofPTH [7]. Patientswith CKD generallyrequireamultimodality treatmentapproach irrespective ofthecauseoftheirkidney disease [8]. The control of hypertension, DM, hyperphosphatemia (using phosphate binding agents), acidosis (using sodium bicarbonate), fluid overload (with diuretics) and uremia (by uricosurics) are the major pharmacological management targets for patients with chronic kidney disease.

MATERIAL AND METHODS

The present study is a retrospective study performed in the department of Nephrology, Sri Venkateswara Institute of Medical Sciences (SVIMS),Tirupati. The study was conducted between August2017andJanuary2018. A total of 180patientsdiagnosed with chronic kidney disease wereincludedinthestudyandwere further groupedintotwo groupsof90each(those with diabetes mellitus (DM) and those without diabetes mellitus (Non DM)). Inclusion criteria of the study are a) patientsofeithersexofageabove18withchronic kidneydisease and b) patients with and withoutDiabetes 50% each,both male andfemale withappropriate serummarkersof MBD (calcium,phosphate,vitamin D,PTH). The study excluded pregnant women, patients below 18 years of age,patients without CKD and patients on dialysis.

Data Collection

Thestudywasstartedafter obtainingapprovalfromInstitutional ResearchEthics Committee, SVIMS. Patients'case sheetswere selectedbasedupon inclusionandexclusioncriteria fromthe MedicalRecordsDepartmentafterobtaining permissionfrom MedicalRecordsOfficer, SVIMS.The data wascollectedusing study materialsforsixvisitswithanapproximateintervalofsix monthsbetween visits of the patients with CKD whoareonfollowupforthe past3years(2015-2017). The laboratoryparametersincludingserumcalcium, serum phosphate, vit-DandPTH from bothDMandNon-DMpatientswere collectedforsixvisits, however, data obtained

during the first (baseline) and last (conclusion) visit were used for analysis. Estimated glomerular filtration rate (eGFR) was calculated using modification of diet in renal disease (MDRD) formula [9].

Statistical Analysis

Data was recorded on a pre-designed proforma and managed using Microsoft Excel worksheet. Data was expressed in terms of mean ± standard deviation (SD) and median (interquartile range) depending upon the distribution of data. Values were presented as counts and percentage. Comparison of parameters at baseline and conclusion was done by using students unpaired t test or Mann Whitney U test, as appropriate. A p value <0.05 was considered statistically significant. Statistical analysis was done using Microsoft excel spread sheets and statistical package for social sciences, SPSS for windows version 16.0.

RESULTS

Table-1. Gender distribution of the study groups

Gender	Diabetes mellitus	Non-diabetes mellitus	Total (%)
Male	60	62	122 (67.8)
Female	30	28	58 (32.2)
Total	90	90	180 (100)

Table-1 shows the gender distribution of the study groups. Among CKD patients with diabetes, malesandfemalesaredivergentwith60male and30femalepatients.Innon-DMpopulation,majorityofthepatients(62)werefound to bemalesand femaleswere 28 in number.

Table-2.Demographic data and parameters studied in patients with CKD (n=180)

Parameters	Baseline	Conclusion	p-value
Calcium (mg/dL)	9.26 ± 0.92	9.48 ± 0.81	0.019*
Phoshorus (mg/dL)	3.92 ± 0.80	3.88 ± 0.80	0.627
Ca X P	36.23 ± 7.95	38.39 ± 25.27	0.274
eGFR (mL/min/sq m)	31.08 ± 17.56	27.00 ± 14.53	0.017*

Data expressed as mean ±SD; *statistically significant

BMI=body mass index; Ca X P=product of calcium and phosphorus, eGFR=estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula

Table-2 shows the demographic data and the biochemical parameters studied in all the patients at base line and at conclusion. The mean age of the patients was 58.66 years and BMI was 25.07 Kg/m^2. Serum calcium levels were significantly increased and eGFR was significantly decreased at conclusion compared to baseline.

Table-3.Demographic data and parameters studied in CKD patients with and without diabetes mellitus

Parameter	CKD patients with Diabetes mellitus			CKD patients without Diabetes mellitus		
	Baseline	Conclusion	p-value	Baseline	Conclusion	p-value
Calcium (mg/dL)	9.35 ± 0.70	9.44 ± 1.02	0.501	9.18 ± 1.10	9.52 ± 0.53	0.009*
Phosphorus (mg/dL)	3.96 ± 0.84	3.93 ± 0.76	0.823	3.88 ± 0.77	3.83 ± 0.85	0.645
Ca X P	36.98 ± 8.34	36.87 ± 7.23	0.928	35.48 ± 7.52	36.30 ± 7.57	0.467
eGFR ($mL/min/m^2$)	32.88 ± 14.68	27.74 ± 12.72	0.013*	29.28 ± 19.96	26.26 ± 16.19	0.267

Data expressed as mean ±SD; *statistically significant

BMI=body mass index; Ca X P=product of calcium and phosphorus; eGFR=estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula

Table-3 shows the demographic data and the biochemical parameters studied in CKD patients with and without diabetes mellitus at base line and at conclusion. The average age and BMI of CKD patients with diabetes mellitus were 62.22 years and 25.76 Kg/m^2, respectively. The mean age and BMI of patients without diabetes mellitus were 55.10 years and 24.39 Kg/m^2, respectively. Serum calcium levels were significantly increased at conclusion in CKD patients without DM and eGFR was significantly decreased at conclusion compared to baseline in CKD patients with DM.

Table-4.Markers of CKD MBD in patients with CKD (N=19)

Parameter	Baseline	Conclusion	p-value
Calcium (mg/dL)	9.47 ± 0.61	9.55 ± 0.70	0.697
Phosphorus (mg/dL)	3.88 ± 0.82	4.02 ± 0.98	0.644
Ca X P	36.60 ± 7.04	38.13 ± 8.44	0.547
Vitamin-D (ng/mL)	26.29 ± 11.93	33.85 ± 18.12	0.138
PTH(pg/ml)	86.07 ± 105.26	53.12±42.64	0.214
eGFR (mL/min/m^2)	34.24 ± 18.68	28.26 ± 13.53	0.266

Data expressed as mean ±SD; Ca X P=product of calcium and phosphorus; PTH=parathyroid hormone; eGFR=estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula

Table-4 presents the vitamin D and parathyroid hormone levels of CKD patients both at baseline and at conclusion. No significant difference was observed for any of the study parameters between the baseline and conclusion levels.

Table-5.Untreated (UT) and treated (T) CKD patients

Parameter	Diabetes mellitus		Non-Diabetes mellitus	
	Base line	Conclusion	Base line	Conclusion
Phosphate Binders (UT)	65	59	59	50
Phosphate Binders (T)	25	31	31	40
Calcium Acetate (UT)	68	61	65	62
Calcium Acetate (T)	22	29	25	28
Sevelamer (UT)	87	88	84	78
Sevelamer (T)	3	2	6	12
Vitamin-D analog (UT)	40	27	43	26
Vitamin-D analog (T)	50	63	47	64
Calcium Supplements (UT)	82	81	79	82
Calcium Supplements (T)	8	9	11	8

DISCUSSION

Regulation of mineral metabolism is one of the important functions of kidneys. Several factors such as parathyroid hormone, fibroblast growth factor 23 and vitamin D are actively involved in mineral metabolism through their effects on kidneys. Hence, disturbancesofboneandmineralmetabolismarecommon in chronic kidney disease and the resultingCKD-MBDleadstoabnormalities inserumphosphate,calcium,productofcalcium and phosphateandPTHwhichcausevarious adversecardiovascularеventsand increasedmortalityin course of time in patients with chronic kidney disease. Pharmacologicaltherapy isveryessentialtocontrolhyperphosphatemia, hyperparathyroidism, abnormalities in serum calcium and vitamin-D levels in CKD patients. Findings of earlier studies wereunclearbecauseofthe variations inthemanagement of CKD-MBD;hence, the present study evaluated the effect of treatment on serum levels of CKD-MBD parameters.

The present study is a retrospectivestudyconductedon180 patients with chronic kidney disease.SerumlevelsofCKD-MBDmarkers such as calcium, phosphate,vit-Dand PTHand the specific therapeutic outcomesof these parameters with pharmacological management were studied. Patientswhowere onfollowupfor at least3years(2015-2017)wereincluded into the study andserumparameterswere measured during every visit at sixmonths intervalduring the study period.Firstvisitwastaken asbaselineandsixthvisit asconclusion. In a multicenter study by Gallieni et al., the management of CKD-MBD was evaluated at two visits, however, the visits were 6 months apart [10].In the present study, all the180patients werefurther classifiedinto two groups of 90 each based on the presence or absence of diabetes mellitus.

When the gender distribution was considered, in the present study it was found that in both groups of CKD patients (with and without diabetes mellitus), males were in larger number compared to females (table-1), the incidence of CKD-MBD is more common in males compared to females (67.8%vs 32.2%). Similar findings were reported in earlier studies. Jallah et al., in their observational study on the management of patients with CKD-MBD reported that 57% of their study population were males and 42% were females [11].CKD-MBD gradually progressed in its extremity with the age. The mean age of CKD patients in the present study was 62.22±10.30for patients with diabetes mellitus and 55.10±12.67 for patients without diabetes mellitus. Jallah et al., have reported an age incidence for CKD-MBD patients as 68.0±13.9 and 70.9±14.1 [11].The pharmacological management in the present study was mainly focused on the serumlevelsofcalcium,phosphate,vit-Dand

PTH.Hence, patientswereprescribed withcalciumsupplements,phosphatebindersand vit-Danalogues and were evaluated.

Serum calcium levels were found to be increased (p=0.019) and eGFR was decreased (p=0.017) at conclusion when compared to baseline levels in all the patients with CKD. On the other hand, serum phosphorus levels and product of calcium and phosphorus were maintained throughout the study period (p=0.627 and p=0.274 for phosphorus and product of calcium and phosphorus, respectively) (table-2).

Further evaluation was done by categorizing the patients into those with diabetes mellitus and without diabetes mellitus. Serum calcium was significantly increased at conclusion compared to baseline (p=0.009) in patients without diabetes, however it remained unchanged in patients with diabetes mellitus (p=0.501). Serum phosphorus and product of calcium and phosphorus were similar at baseline and at conclusion in both diabetes and non-diabetes patients (table-3). Data on vitamin D and parathyroid hormone was available for 19 patients. When analyzed, no significant difference was observed in any of the parameters studied (table-4).

The rate of GFR decline is often relatively constant overtime in an individual patient, but the rate of GFR decline is highly variable when compared among patients, ranging from slowly progressive over decades to rapidly progressive over months. In the present study,eGFR values of all the patients at baseline and conclusion were calculated using MDRD equation and it was found that the GFR levels were declined in spite of pharmacological intervention in both diabetes and non-diabetes groups of CKD patients. However, the decline was more significant in CKD-MBD patients with diabetes mellitus (p=0.013) whereas it remained unchanged in patients without diabetes (p=0.267) (table-3).

In the progression of chronic kidney disease, several factors apart from the native disease such as anemia, infections, hypertension, proteinuria, diabetic status, hyperuricemia, dyslipidemia and abnormal mineral metabolism play an important role. Inacohortstudy,during thefollow-upamong1682participantswith type 2 diabetes mellitus, 263(15.6%) individualshada rapideGFRdecline which was definedas4.0%peryear [12].In the present study, the average decline ineGFRduring the study period which was 3 years was found to be 15.6% in patients with diabetes; in CKD MBD patients without diabetes, the eGFR decline was found to be 10.3%.This indicates that in spite of pharmacological intervention, there was progression of CKD especially in patients with diabetes, however the rate of progression was slower in patients without diabetes mellitus.

The data on pharmacologicalmanagementwascollectedfrom the case sheetsfor threedifferentvisitsdependinguponpatients'follow-up.Management of CKD patients in the presentstudy wasmainly done using phosphate binders(such as calcium acetateandsevelamer), calciumsupplements andvit-Danalogues. The number of patients who are treated and untreated with phosphate binders, calcium supplements and vit-D analogues in CKD patients was shown in table-5. The number of untreated patients is high for all the drugs except vitamin D analogues in both subgroups of CKD patients. Thus, majority of the patients were managed by dietary measures and if the general measures do not help to control the disturbances, patients were managed with phosphate binders.

Limitations of the study

The present study has few limitations. Sample size was small and the duration of study period was short which could have resulted in insignificant p value for some of the parameters. Data for vitamin D and parathyroid hormone was available for nineteen subjects as the study was mainly based on specific lab parameters that reflect the kidney function. The study was retrospective single center study and hence the results may not be applicable to entire Indian population.

Conclusion

Serum calcium, phosphate and product of calcium and phosphorous levels were maintained in both the CKD groups with pharmacological intervention by phosphate binders.The pharmacological interventions in the form of phosphate binders, vit-D analogues and calcium supplements also helped in maintaining the GFR during the period of 3 years (2015-2017) with no significant decline.Thus, based on the observationsof the present study, it can be concluded that pharmacological intervention in CKD patientsrenders effective management for MBD by maintaining serum calcium, phosphate and calcium phosphorous product status.

REFERENCES

[1] A.S. Levey, R. Atkins, J. Coresh, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes.Kidney Int., 2007, 72:247-59.

[2] A.K. Singh, Y.M. Farag, B.V. Mittal, et al. Epidemiology and risk factors of chronic kidney disease in India – results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. BMC Nephrol., 2013,14:114.

[3] J. T. Dipiro, R. L. Talbert, G. C. Yee, et al. Pharmacotherapy a Pathophysiologic Approach. Seventh Edition, McGraw-Hill Companies, 2009, p747-751, 757.

[4] H.Komaba, M. Tanaka, M. Fukagawa. Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Internal Medicine., 2008, 47:989-994.

[5] K. S. Schonder. Pharmacotherapy Principles and Practice. McGraw-Hill Companies, 2008, p 373,374, 377.

[6] S. M. Moe,et al. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Official Journal of The International Society of Nephrology.,2009, 76(Suppl:113):S3-S4.
[7] R. Lewis. Mineral and bone disorders in chronic kidney disease: new insights into mechanism and management. Ann ClinBiochem., 2012, 49:432-40.
[8] UK ProspectiveDiabetesStudy(UKPDS) Group.Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).Lancet.,1998, 352:837-53.
[9] C.M. Florkowski, J.S. Chew-Harris. Methods of Estimating GFR - Different Equations Including CKD-EPI. ClinBiochem Rev., 2011, 32:75-9.
[10] M. Gallieni, N. De Luca, D. Santoro, et al. Management of CKD-MBD in non-dialysis patients under regular nephrology care: a prospective multicenter study. J Nephrol., 2016, 29:71-8.
[11] B.P.Jallah, M. H. M.Raasveld, B. V. Dam. Cost Effective Management of CKD-MBD: An Observational Study. International Journal of Nephrology and Kidney Failure.,2015, 1:1.
[12] G. Zoppini, G. Targher, M. Chonchol, et al.Predictors of Estimated GFR Decline in Patients with Type 2 Diabetes and Preserved Kidney Function. Clin J Am SocNephrol., 2012,7:401-8.