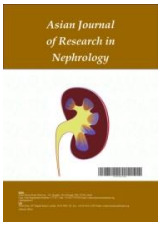

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Assessment of Treatment Pattern for Management of Hyperphosphatemia in Maintenance Hemodialysis Patients: A Prospective Observational Comparative Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AR and SG designed the study and performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MJ and EA managed the analyses of the study along with literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hyperphosphatemia is a common complication of End-Stage Renal Disease (ESRD) associated with fluctuating serum levels of phosphorus, calcium, para thyroid hormone (PTH), and metastatic calcification. Based on the calcium-phosphorus level, patients may receive Calcium free or calcium-based drugs with phosphorus restricted diet.
Objective: To assess the treatment modalities for the management of hyperphosphatemia.
Methodology: A Prospective-observational-comparative-multivariate study, conducted in a tertiary care teaching hospital located in Ernakulam district of Kerala, in India for a period of 6 months. All patients admitted for Hemodialysis(HD) with ESRD and those aged above 35 were included in the study based on pilot study. Baseline data were obtained at the study entry by utilizing a semi-structured questionnaire, followed by the laboratory values of phosphorus, calcium, inter dialytic weight gain (IDW), medications, etc. from their treatment record. The patient's adherence behaviour was evaluated by using the international disease-specific ESRD adherence questionnaire.

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Results: Data from 53 cases indicates that, treatment given for management of hyperphosphatemia was not rational, not based on serum levels of calcium and phosphorus. The majority of the population prescribed with calcium-free phosphate binder-sevelamer and only 28% of the population is having controlled serum calcium and phosphorus levels. Poor economic status, a major factor contributing to the low adherence to the medications.
Conclusion: Socio-demographic factors statistically do not influence treatment patterns, but annual income correlates with poor drug adherence. For the management of hyperphosphatemia, sevelamer, and calcium-based calcium carbonate and/or calcium acetate were prescribed in this study population. Poor adherence to the diet was found to be the main cofounding factor for hyperphosphatemia.

Keywords: Hyperphosphatemia; haemodialysis; hypercalcemia; adherence; phosphate binder.

1. INTRODUCTION

End-stage renal disease is a medical condition in which the person's kidney ceases functioning permanently leading to the need for a regular course of long-term dialysis or a kidney transplant to maintain life [1]. Hyperphosphatemia is a characteristic feature of chronic kidney disease-mineral and bone disorders. Haemodialysis patients, having the risk of cardiovascular events and accelerated atherosclerosis which occur as the complication of abnormal calcium-phosphorus metabolism and dyslipidemia apart of hypertension [2]. The clinicians who treat the patients with ESRD, their major goal of therapy is the safe and effective management of serum electrolyte levels [3]. Consequences of inadequately controlled phosphorus, calcium may include aortic calcifications, bone mineral disorders, and secondary hyperparathyroidism (HPTH) [4]. However, Management of hyperphosphatemia is challenging and a multifaceted approach consisting of dietary phosphorous restriction, dialysis, oral phosphate binders, sometimes there is a need for a topical agent to manage skin itching conditions and control of HPTH [5].

For hemodialysis patients, a typical phosphorous restricted diet includes ~ 900 mg of phosphorous per day of which ~371mg is absorbed. Additional means of phosphorous limitation are necessitated, and most ESRD patients require the use of phosphate binders. Different types of phosphate binders have different phosphate-binding capacities and therefore it also associated with varying pill burden [6].

Many studies conducted recently show that the presence and severity of calcification of coronary arteries is the major predictor of mortality in those who are new to dialysis and calcium-based drugs show more mortality rate than the sevelamer [7]. Currently, several phosphate binders are available in the market, each with its potential advantages and disadvantages. Calcium based drugs are inexpensive but their use is confined to the development of hypercalcemia and it is usually given for those with hyperphosphatemia and hypocalcaemia. Non – calcium-based drugs such as sevelamer and lanthanum are expensive and are associated with gastrointestinal side effects. These calcium free phosphate binders are usually prescribed for those having normal calcium level along with elevated phosphorus level. More recently hyperphosphatemia has also been controlled by iron-based phosphate binders. As Vit D is indirectly associated with the serum calcium level, as it one of the cofactor needed for absorption of calcium it also affects the treatment of hypocalcemia [8].

Different phosphate binders show differences in their overall long term and short-term effectiveness, mode of action, composition, and tolerability. Poor adherence is common in ESRD, is a well-established obstacle to treatment success [6,9,10]. Besides, the recent advances in therapy, achievement, and maintenance of guidelines recommendations for hyperphosphatemia remain inadequate. Usually, the selection of phosphate binders should be based on serum levels of calcium, phosphorus, PTH, Vit D, etc. Non-compliance to dietary restrictions, phosphate binders, inadequate dialysis, financial limitations may also account for inappropriate control of serum phosphate [8]. The present study aims to demonstrate various treatment modalities for the management of hyperphosphatemia and to evaluate the appropriateness of treatment.

2. MATERIALS AND METHODS

This was a prospective observational comparative study conducted in a tertiary care teaching referral hospital located at Ernakulam, Kerala and the work done for a period of 6 months (August 1-2018 to January 31-2019). All patients who were undergoing maintenance hemodialysis for at least three months were screened for the study. Adults aged below 35 years, acute renal failure cases, and patients with hepatitis C and HIV were excluded from the study. The aim and protocol of the study were explained to each participant orally and they were given with 2 days time to decide on whether to participate or not to participate

Baseline data regarding the patient demographics, comorbidities, and data on dialysis treatment were obtained by using a semi-structured questionnaire by interviewingthe patient and bystander, followed by the information on the laboratory values of the serum levels of phosphorus, calcium, interdialytic weight gain, medications, etc. from their treatment record. The patient's adherence to the treatment regimen including dialysis schedule, diet, fluids, and medications was evaluated by using the international disease-specific ESRD adherence questionnaire. The medications which were taken for the management of hyperphosphatemia were only considered into the study. For the analysis of the data, the study population were classified into seven classes and all of the further investigations and comparisons were done based on the treatment they have taken. Based on scoring for the ESRD Adherence Questionnaire, adherence towards dialysis schedule, diet, fluid and medication were evaluated, by classifying the study group into three domains such as high, moderate and low adherent patients.

2.1 Statistical Analysis

Data was collected and compiled by using Microsoft excel and statistical work was done by the statistical package for social science (IBM SPSS 20). Continuous variables were expressed by mean and standard deviations as appropriate. The level of significance between the two variables was determined by the methods of students T-test and one-way ANOVAs. The correlation between two discrete variables was analyzed by the Spearman rank correlations and Pearson's chi-squared as applicable. Sociodemographic details including age, gender, years on dialysis, qualifications, presence of comorbidities are expressed by the means of mean, standard deviation, in percentage followed by the diagrams. While evaluating the significance, the P-value of less than 0.05 was considered to be statistically significant.

3. RESULTS

Out of 96 patients who were enrolled, only 53 patients were selected for the study based on the inclusion and exclusion criteria and consented by patient for the research. These selected populations were categorized into the seven groups based on the medications they were taking and appropriateness of treatment regimen were evaluated along with monitoring the serum levels of calcium and phosphorus.

All the further study was based on seven categories that represented the treatment pattern followed for hyperphosphatemia management (Fig. 1). It was observed that 23% of patients were taking the drug sevelamer alone, 16.90% on combinations of sevelamer and calcium acetate, 15.10% received sevelamer and calcium carbonate, 13% on combinations of calcium acetate and vitamin D, 9% calcium carbonate alone, 15% were on calcium carbonate and vitamin D and 7.50% were not under any kind of treatment.

The study represented a high prevalence of hemodialysis cases in males (42 patients representing 79%) while compared to female represented by 21% cases (Table 1). The study recorded the cases with age above 35 years only, and all the patients included in the study were sorted into two groups i.e. 35 – 60 years and >60yrs, then the age was converted into the mean and standard deviation under all the seven groups. It was also observed that 66% of patients were above 60 years of age and 34% were between the age of 35 and 60, indicating the increase in the prevalence of kidney associated diseases as people grow old.

The qualifications of the patients in the study represented that 49% had high school education followed by 28.3% with Higher Secondary School (HSS), and only 22.7% were having a degree from college. Thus, indicating the influence of education in progression or disease development. The patient's years on hemodialysis were explained as the mean and standard deviation in these seven groups. The patients undergoing dialysis were separated and represented as either twice or thrice weekly, the data suggested a predominance of twice-weekly schedule under this study.

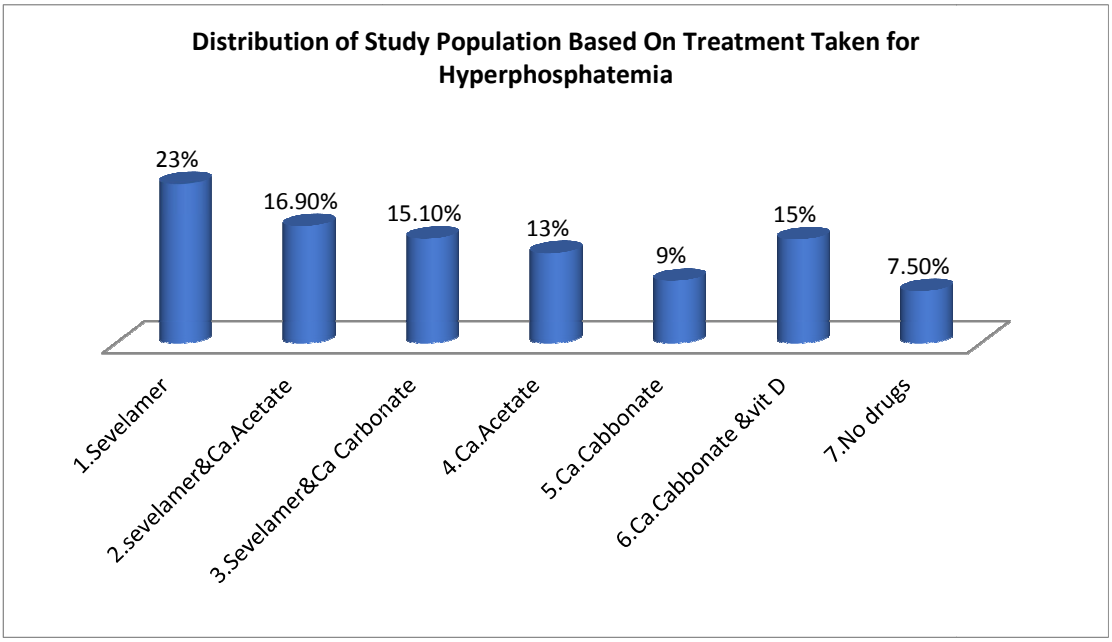

Fig. 1. Distribution of the population in the seven categories such as those taking sevelamer alone, combination of sevelamer and calcium acetate, combination of sevelamer and calcium carbonate, calcium acetate alone, calcium carbonate alone, and combination of calcium carbonate and vitamin D based on the treatment taken for the management of hyperphosphatemia

Table 1. Defines patient demographic details represented in the seven groups of the study population

parameters	1	2	3	4	5	6	7	%
No. of patients	16	9	5	6	5	8	4	100
Gender								
Females	4	2	1	2	1	1	0	21
Males	12	7	4	4	4	7	4	79
Age								
35-60 yrs	55.42 ± 2.87	52.83 ± 8.23	57	45	48±8	50	58.5 ± 0.5	34
>60 yrs	65.85 ± 3.44	69 ± 5.52	75.33 ± 5.3	68.2 ± 6.11	68.2 ± 6.11	62.66 ± 1.69	68.5 ± 0.5	66
Qualification								
High school	8	5	4	1	2	4	2	49
HSS	5	3	1	2	2	1	1	28.3
College	3	1	0	3	1	3	1	22.7
Years on HD	3.03 ± 2.4	2.87 ± 2.04	2.62 ± 1.91	4 ± 3.69	3.2 ± 3.42	5.06 ± 3.57	3.25 ± 1.9	-
Dialysis schedule								
Twice/ week	5	3	3	4	3	2	1	39.6
Thrice/week	11	6	2	2	2	6	3	60.4

On analysing the major co-morbidities, it was found that hypertension, diabetes, dyslipidemia, and coronary artery disease were the major contributors to the development and progression of the disease (Fig. 2). The work also focussed on interdialytic weight gain (IDW) and dialysis schedule, students T-test was applied to recognize the significance, the P-Value of 0.412

indicated no statistical significance id existing between the two parameters.

Based on the serum level of phosphorous and calcium, the study population was subdivided into five groups which are showcased in Fig. 3, it indicates that only 28% of the population had controlled serum level of phosphorus and calcium.

To define the significance between the drug adherence and annual income, patients were classified based on annual income such as below 1 lakh and above 1 lakh followed by adherence towards drug such as high, moderate and low. Spearman's rank correlation and Pearson's correlation statistical tests were applied to study the correlation between these two parameters (Table 3). This indicated positive correlation of annual income towards drug adherence and proved that low annual income was one of the major causes of the poor adherence to the drug in haemodialysis patients, a similar correlated response was obtained while the patient was interviewed.

The study also evaluated the serum level of calcium and phosphorous while treatment was suggested in the management of hyperphosphatemia. One Way ANOVA was applied in this study (Table 4), and the P-value obtained (0.53) indicated that there is no statistical significance that existed between the calcium level and seven categories of treatment given, thereby we can convey that the treatment for hyperphosphatemia provided, whether calcium-based or calcium-free was not based on the serum level of calcium. The evidence is also illustrated diagrammatically (Fig. 4), which explains that "only6% of the population is under the risk of elevated serum levels of calcium, whereas 56% of the population were having hypocalcemia.

Table 2. Demonstrate the significance between the IDW and dialysis schedule

Dialysis	No. of Patients	Mean	Standard Deviation	Statistical Test Used	P Value
Twice Weekly	21	2.7933	0.6870	Student T Test	0.412**
Thrice Weekly	32	3.0813	1.64913	(C I * =0.95)	

Confidence Interval
***Not statistically significant*

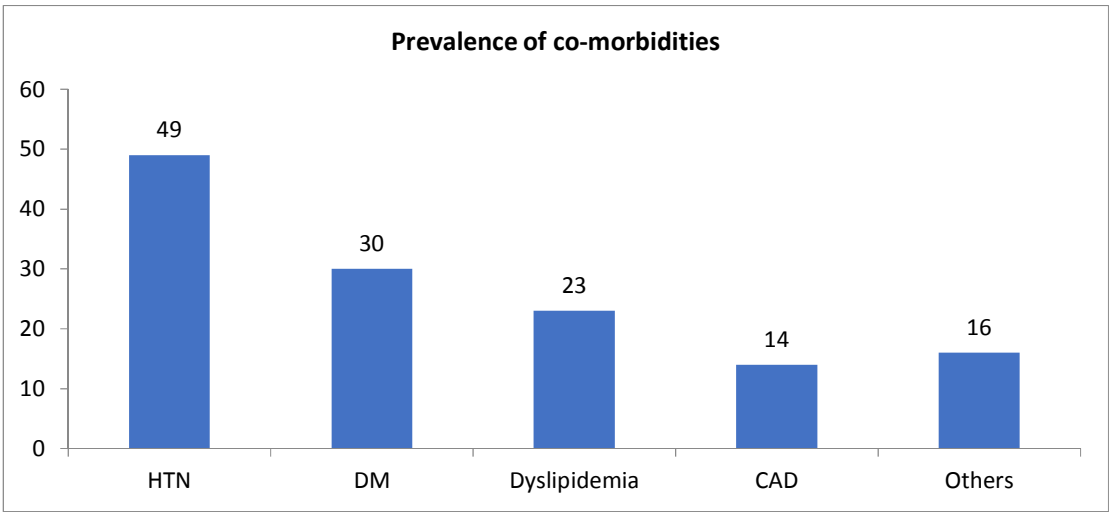

Fig. 2. Represents the prevalence of the comorbidities among the study population with the high prevalence of hypertension followed by diabetes, coronary artery disease, dyslipidemia, and others

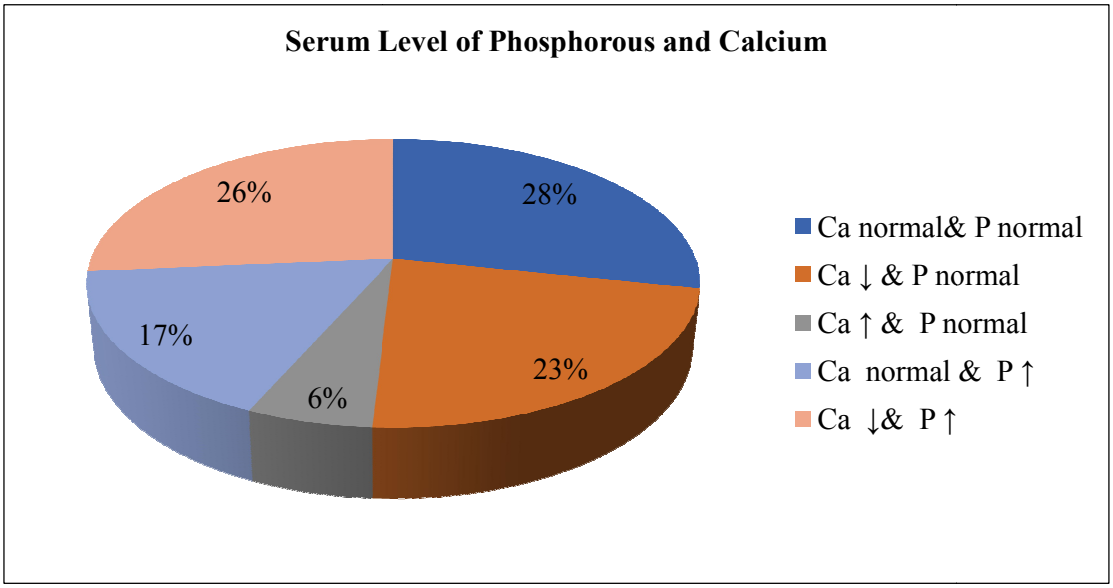

Fig. 3. Categorization based on serum level of phosphorous and calcium

Table 3. Correlation between drug adherence and annual income

Drug adherence → / Annual income ↓	High adherence	Moderate adherence	Low adherence	Total	Statistical test	Correlation coefficient value
Below 1 lakh	7 (13.20%)	13 (24.52%)	5 (9.43%)	25 (47.17%)	Spearman's Rank	0.276*
Above 1 lakh	18 (33.96%)	8 (15.09%)	2 (3.77%)	28 (52.83%)	Pearson's Correlation	0.259*
Total	25 (47.17%)	21 (39.62%)	7 (13.20%)	53 (100%)		

**shows a positive correlation*

Table 4. Distribution of the study population in seven groups based on the serum level of calcium

Category	1	2	3	4	5	6	7	Total	Statistical Test Used	P Value
Hypocalcemia	7	6	3	5	1	4	3	29	One	
Normocalcemia	9	3	1	1	4	2	1	21	WayANOVA	0.53**
Hypercalcemia	0	0	1	0	0	2	0	3	F = 2.270	
Total	16	9	5	6	5	8	4	53		

*** Not statistically significant*

For the purpose of evaluation (Table 5), the patients were classified according to the phosphorus level such as hypophosphatemia, normophosphataemia and hyperphosphatemia along with adherence behaviour toward diet, which were catagorised as high, moderate and low adherent. The statistical significance between the phosphorus level and diet adherence, the values suggested a highly statistically significant relationship existed between the diet adherence and phosphorus level, which directly pinpoints that, one of the major reasons for the elevated serum levels of phosphorus is the poor adherence to the restricted diet regimens. This could directly be linked to increased phosphorus level as a factor of non-adherence to the diet plan suggested.

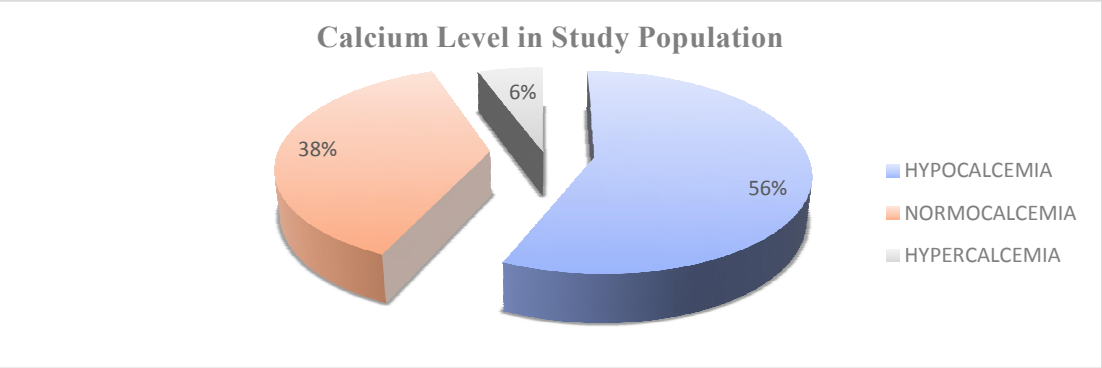

Fig. 4. Distribution of the study population on calcium level

Table 5. Data regarding the significance between the phosphorus level and diet adherence

Phosphorus Level	Diet Adherence			Total	Statistical Value	P-Value
	High	Moderate	Low			
HYPO	0	0	0	0	One Way ANOVA	0.003***
NORMAL	9	13	5	27		
HYPER	3	9	14	26		
TOTAL	12	21	19	53		

****denotes highly statistically significant*

4. DISCUSSION

Hyperphosphatemia is one of the major complications that occur in the maintenance hemodialysis patients, which is also the leading cause of secondary hyperparathyroidism, cardiovascular mortalities, and bone diseases. Phosphorus is having second place as a most abundant element in the human body after calcium. It mainly occurs as the hydroxyapatite in bones and teeth, 14% located as organic compounds intracellularly, 1% extracellularly, 1% located in the vascular space followed by 20% as protein bound. There is a significant interaction between factors that influence calcium and phosphorus homeostasis. Parathyroid hormone and Vitamin D are the major regulatory mediators [9]. Treatment for the hyperphosphatemia should be based on the serum levels of phosphorus, calcium, and parathyroid hormone, it can be treated with the calcium-free and calcium-based phosphate binders. This study was conducted to evaluate the prescribing pattern for the management of hyperphosphatemia and to evaluate the appropriateness of the treatment regimen. The demographics details on correlation with the study conducted by Balasubramanyan et.al [10] indicated that the mean age in this study (62.32±3.44) was higher than the reference, whereas the predominance of male gender was same in both the study. The main reason for the male predominance might be due to social habits like alcoholism, smoking, and other habit-forming substances used or practices leading to a negative impact on health.

The majority (60.37%) of the study population followed the twice-weekly dialysis schedule and most of the patients show reluctance to thrice-weekly schedule because of unaffordable dialysis costs, even when it was needed the most by them. Hypertension was the highly prevalent comorbidity in this study population followed by diabetes, dyslipidemia, and Coronary Artery Disease (CAD). In this study population, 28% of the patients had controlled serum level of calcium and phosphorus. while checking the adherence of the patients to the drugs it was found that about 38% of the population showed the poor adherence, and it had a positive correlation to the annual income status, that is low economic status was the major cause of poor drug adherence.

Thus for the management of hyperphosphatemia, either calcium-based or calcium-free phosphate binders can be given, where the drug opted should be based on the serum levels of calcium apart from the phosphorus, but in our study, the P-value tested to determine the significance between the

calcium level and drugs taken showed that, there is no sign which implies inappropriateness of the treatment given to the patients [11]. This study also indicated that 56% of the population under study had a risk of hypocalcemia and 6% had hypercalcemia. A similar type of reporting is also done by Yi-Wen Chiu et. al. [12] stating the poor adherence to diet as the major contributing factor for the elevated serum levels of phosphorus, which is also depicted in this study, showing the positive correlations between the diet adherence and phosphorus level.

This study's drawback was the limitation in the population; thus, this could be taken as a pilot study and the work may be extended into a large group of patients. A larger sample size can give a precise result. Also, the data regarding the patient's adherence to the drugs and diet, etc.were collected by means of interviewing the patients, hence it may involve a component of bias.

5. CONCLUSION

Fluctuating serum levels of calcium and phosphorus is one of the major complications that occur in ESRD patients. A positive outcome is based on the proper treatment of hyperphosphatemia which in turn is based on the levels of calcium and phosphorus. The treatment pattern followed for this study population was not strictly based on the serum level of calcium and phosphorus.. The annual income or family income was the only factor which had influence on treatment pattern and it was observed to have influence on the drug adherence and treatment schedules. This study indicated that for the management of hyperphosphatemia along with serum calcium level control, a calcium-based – calcium carbonate or calcium acetate and calcium-free – sevelamer can be given.. The study also revealed that restriction of diet rich in phosphorus is required for effective control of phosphorus level.

CONSENT AND ETHICAL APPROVAL

After approval from the institutional ethics committee, the sample size was calculated scientifically and out of 96 patients undergoing hemodialysis who were enrolled into this study by random sampling method, only 53 patients who met the study criteria were included into the study. Verbal and written consents were taken from the patients who were included in the study by providing them with a consent letter in the local language.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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