

## Original Article

## Evaluation of polypharmacy and adherence to the phosphorus binding treatment in hemodialysis patients

*Hemodiyaliz hastalarında polifarmasi ve fosfor bağlama tedavisine uyumun değerlendirilmesi*Nihal Bozdağ Kaplan<sup>1\*</sup>, Nurol Arık<sup>2</sup><sup>1</sup> Department of Internal Medicine, Yeni Yüzyıl University Medical Faculty, İstanbul/ TÜRKİYE<sup>2</sup> Division of Nephrology, Department of Internal Medicine, Ondokuz Mayıs University Medical Faculty, Samsun/ TÜRKİYE

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## Abstract

**Background:** Polypharmacy and nonadherence to treatment regimens confront as an ever-mounting problem in hemodialysis patients. The aim of the present study was to emphasize the importance of polypharmacy and tablet load problem and to evaluate the adherence to phosphorus binding agent treatment and to examine the factors that cause to non-adherence. **Material and Method:** 361 patients who were in regular dialysis program in 4 different hemodialysis centers in Samsun city were included in the study. By meeting face to face, a questionnaire that was composed of 35 questions which investigated the factors that effect the polypharmacy and treatment adherence was filled to patients by a physician. Adherence to phosphorus binding treatment was measured according to both serum phosphorus level and Modified Morisky Adherence Scale. **Results:** In hemodialysis patients, the mean daily used drug groups were found as 5, the tablet count was found as 10. It was determined that the phosphorus levels of % 40.4 of patients who were using phosphorus binding agents were found above the target phosphorus level that was recommended in the guidelines. According to the adherence questionnaire that was performed to the patients, non-adherence rate to the phosphorus binding agents was found 77,3 %. In addition, age, educational background, smoking and tablet load are the factors that were not found effective on the adherence to the phosphorus binding agents treatment. **Conclusion:** Polypharmacy and non-adherence to the phosphorus binding treatment are serious and worth-stressing problems that should be solved in hemodialysis patients. We think that more, more advanced and quality research is needed to improve adherence on this subject

**Keywords:** Adherence ,hemodialysis, phosphorus binding treatment, polypharmacy

## ÖZ

**Amaç:** Hemodiyaliz hastalarında polifarmasi ve tedavi rejimlerine uyumsuzluk giderek artan bir sorun olarak karşımıza çıkmaktadır. Bu çalışmanın amacı hemodiyaliz hastalarında polifarmasi ve tablet yükü sorununun önemini vurgulamak ve fosfor bağlayıcı ilaç tedavisine uyumu değerlendirmek ve uyumsuzluğa neden olan faktörleri incelemektir. **Materyal ve metod :** Samsun ilinde bulunan 4 ayrı hemodiyaliz merkezinde düzenli diyaliz programında olan 361 hasta çalışmaya alındı. Hastalarla yüz yüze görüşülerek, polifarmasi ve tedaviye uyumuna etki eden faktörleri araştıran 35 sorudan oluşan anket bir doktor tarafından dolduruldu. Fosfor bağlayıcı tedaviye uyum hem serum fosfor düzeyine göre hemde Modifiye Morisky uyum skalasına göre ölçüldü. **Bulgular:** Hemodiyaliz hastalarında günlük kullanılan ilaç grubu ortalama 5, tablet sayısı ise 10 bulundu. Fosfor bağlayıcı ilaç kullanan hastaların %40.4' ünün fosfor düzeylerinin kılavuzlarda önerilen hedef fosfor düzeyinin üstünde olduğu saptandı. Hastalara uygulanan tedaviye uyum anketine göre ise fosfor bağlayıcılara uyumsuzluk oranı %77,3 bulundu. Ayrıca yaş, eğitim durumu, sigara kullanımı ve tablet yükü fosfor bağlayıcı ilaç tedavisine uyumda etkili bulunmamıştır. **Sonuç:** Hemodiyaliz hastalarında polifarmasi ve fosfor bağlayıcı tedaviye uyumsuzluk üzerinde durulması ve çözülmesi gereken ciddi bir sorundur. Bu konuda uyumu artırmak için daha fazla, daha gelişmiş ve kaliteli araştırmalara ihtiyaç olduğunu düşünüyoruz.

**Anahtar kelimeler:** Fosfor bağlayıcı tedaviye uyum, hemodiyaliz, polifarmasi

## Highlights

- Polypharmacy will continue to be a more important problem in the future.
- To prevent this, studies should be conducted for effective combined treatment regimens

## Introduction

Human lifespan is getting longer, so the elderly will use more drugs and polypharmacy will continue to be a more important problem in the future. Polypharmacy is associated with high morbidity and mortality as an increasing problem in patients with chronic diseases who have to take long-term drug therapy. In previous studies, polypharmacy has been investigated quite frequently in the elderly and in chronic diseases such as diabetes mellitus, hypertension, hyperlipidemia, AIDS, depression (1,2). However, few studies have investigated polypharmacy in chronic dialysis patients (3).

It has been determined that nonadherence to treatment regimens is common in patients with end-stage renal disease. Most of the studies were performed on hemodialysis patients. Non-adherence to treatment in dialysis patients; It is known to cause results such as increased blood pressure, hyperphosphatemia, hypocalcemia, renal osteodystrophy, anemia, increased risk in terms of drug side-effect reactions and increased drug load. For these reasons, we aimed to measure the extent of polypharmacy in chronic hemodialysis patients and to emphasize the importance of this problem. Another aim of the study is to measure the adherence of chronic hemodialysis patients to phosphorus-binding therapy and to determine the factors affecting adherence.

## METHODS

361 patients who received regular hemodialysis treatment 1,2 or 3 times a week in 4 different hemodialysis centers in Samsun were included in the study. The inclusion criteria's of the study were to have hemodialysis for at least 3 months and to have the mental capacity to understand and answer the questionnaire. The questionnaire was completed by a single doctor by interviewing the patients face to face. The questionnaire was two-stage and included 35 questions. In the first stage, there were questions about the patients' socio-demographic characteristics and polypharmacy. Demographic characteristics of the patients (age, gender, education level, employment status, marital status, income status, who they live with at home), cigarette-alcohol use, chronic kidney disease (CKD) cause, comorbidities, duration of hemodialysis, and how many times a week they underwent dialysis were questioned. The patients were asked about the drug group, type of drug and the number of tablets they used daily, then the results were recorded by looking at the drug boxes they brought with them. The second phase of the questionnaire was conducted only on patients using phosphorus-binding drugs. The second-stage questionnaire included detailed questions related to the patient's understanding of the importance, effect, and side-effect of the phosphorus-binding drug. In addition, the patient was asked questions about which phosphorus binder drug he used at which dose, whether he knew the name, effect and side effects of the drug, from whom he received training about the drug, and the reasons for not taking the drug. The mean of three-month phosphorus measurements and Kt/V values of the patients were recorded. Then, the patients were asked six questions about the Morisky Medication Adherence Scale (MMAS) (4-6). Question 1,2 and 6 in the questionnaire; It measures forgetfulness and inattention. It is thought that it is the determinant of motivation and therefore it will affect motivation in terms of compliance. If the question is 3, 4 and 5; assesses whether patients discontinue medication and understand the long-term benefits of continued therapy. It was thought that these questions were the determinants of knowledge and would affect compliance in terms of knowledge. All questions in MMAS are answered as "yes" and "no". For the motivation domain, each "no" answer gets 1 point, while each "yes" answer gets 0 points. This provides a score in the range of 0-3 for the motivation domain. If the patient's total score is in the range of 0-1, the motivation area is scored as "low". In addition, the score is >1, the motivation area is scored as "high". In the knowledge area, for questions 3 and 4, the answer "no" gets 1 point, while the answer "yes" gets 0 points. In the 5th question, "no" answer gets 0 point and "yes" answer gets 1 point. As a result, a score between 0-3 is obtained for the knowledge domain. If a patient's total score is between 0-1, the information field is considered "low", and if >1, it is considered "high" (**Table 1**). The study has been carried out according to the principles of the Declaration of Helsinki, and its protocol was approved by local ethical committee.

**Table 1 Compliance Questionnaire for Phosphorus Binding Drug Treatment (Modified Medication Morisky Scale)**

Question	Motivation	Knowledge
1-Have you ever forgotten to take your medicine?	Yes (0) , No(1)	
2- Are you careful about the times of taking medication?	Yes (0) , No(1)	
3-Do you sometimes stop taking your medicine when you feel better?		Yes (0) , No(1) )
4-If you feel bad when you take medicine, Would you sometimes stop the medicine?		Yes (0) , No(1)
5-Do you know the long-term benefits of taking your medicine as told by your doctor or pharmacist?		Yes (1) , No(0)
6-Do you sometimes forget to prescribe your medicine on time?	Yes (0) , No(1)	

### Statistical Analysis

Arithmetic Mean±Standard Deviation as the central distribution criterion of the data; As frequency criteria, numbers and percentages were used together. In the data analysis, using the SPSS (Version 12.0) computer program, Student t tests were performed in groups with normal distribution and Mann Whitney U tests were performed in groups that did not comply with normal distribution in pairwise group comparisons. Chi-square test was used to compare the percentages between groups. ANOVA test was used to compare more than two groups. In the study,  $p < 0.05$  was accepted as the level of significance.

### Results

361 patients included in the study, 207 (57.3%) were male and 154 (42.7%) were female. The mean age of the patients was  $57.5 \pm 13.9$  years, and they were between 19-85 years old. Distribution of socio-demographical characteristics by gender of the study participants are listed in **Tables 2**. When the female and male patient groups are compared socio-demographically, it is seen that the rates of lack of education, divorce, not working in an income-generating job and living alone in women are quite high compared to men; however, smoking and alcohol use were found to be low. The most common cause of CKD was hypertension (35%), followed by Diabetes Mellitus (27%). Other causes of CKD are presented in **Table 3**. The mean duration of hemodialysis of the patients was  $52.5 \pm 47.5$  months, and the duration of dialysis of the patients ranged from 3 to 316 months. The mean number of drug groups used by all patients was  $4.2 \pm 1.5$ , and the number of drug groups used daily ranged from 1 to 8. The average number of tablets taken daily, varying between 2-25, was found to be  $9.9 \pm 3.7$  (**Table 4-5**). Considering the drug group and number of tablets of the patients by gender; The mean group of drugs used by men was  $4.1 \pm 1.4$ , women were  $4.4 \pm 1.6$ , and there was no statistically significant difference between them ( $p > 0.05$ ). The average number of tablets used daily was  $9.91 \pm 3.8$  (Range:2-25) in men and  $9.89 \pm 3.6$  (Range:2-20) in women. There was no statistical difference between them ( $p > 0.05$ ).

Of the patients using phosphorus-binding drugs, 90.9% (288 people) stated that they took the drug themselves, and 9.1% (29 people) stated that the drug was given to them by someone else. 83.9% of the patients stated that they took their medication with meals, 10.4% between meals, 5.7% on an empty stomach. While 45.7% (145 people) of 317 patients knew the name of the phosphorus-binding drug, 45.8% did not know the name of the drug, 8.5% (27 people) stated that they could not remember the name of the drug. Only 5.8% (16 people) of the patients stated that they knew about the side effects of phosphorus-binding drugs. 64.7% (205 people) of the patients knew the effect of the phosphorus-binding drug. It was determined that 5.7% (18 people) of the patients in the phosphorus binder group had a medication chart in their hands. Of the patients, 85.5% (271 people) stated that the effect and side effects of the drug were explained by the doctor.

Patients received information about drugs from doctors with 85.5%. Considering the education given to patients about phosphorus binder; 169 (53.3%) patients were informed about the dose/time/duration and purpose of use of the drug. Only education about dose/time/duration was given to 148 (46.6%) patients. The patients were never informed about the side effects and drug interactions of the drug. Of the patients using phosphorus binders, 84.8% (269 people) stated that they did not use the drug regularly, while 15.1% (48 people) stated that they used it regularly. The frequency of regular use of the drug was found to be 15.1% in men and 15.2% in women, and there was no statistically significant difference between them ( $p > 0.05$ ).

We found that the complaints about drug taste were 4 times more common in women than in men, and this difference was statistically highly significant ( $p = 0.002$ ). In addition we found that the complaints about the side effects of the drug were 1.5 times more common in women than in men, and this difference was statistically highly significant ( $p = 0.009$ ).

The reasons for getting tired of using the drug, forgetfulness and drug non-compliance related to tablet size did not differ between the genders ( $p > 0.05$ ). There was no statistically significant difference between the Kt/V values of the patients who used phosphorus binders and those who did not ( $p > 0.05$ ). Only 59.6% of the patients using phosphorus-binding drugs have a phosphorus level below 5.5. Nonadherence to the use of phosphorus-binding drugs was found to be 40.4%. (When serum phosphorus level is taken as a measure of adherence) As seen in **figure 1 and 2**, only 22.7% of the patients scored 4 according to the MMAS. Accordingly, the rate of non-compliance with phosphorus binders was 77.3% according to the patients' self-report questionnaire. While the mean serum phosphorus level of 135 (42.6%) patients using phosphorus-binding drugs and having an MMAS compliance score below 4 was  $5.7 \pm 1.4$  mg/dl, the mean phosphorus level of 182 patients (57.4%) with an MMAS score of 4 was  $5.1 \pm 1.2$  mg/dl and the difference between them was found to be statistically highly significant ( $p = 0.001$ ).

**Figure 1. Modified-Morisky Adherence Scale (MMAS) distribution of patients using phosphorus-binding drugs**

MMAS	Number	%
0	3	0,9
1	42	13,2
2	90	28,4
3	110	34,7
4	72	22,7
Total	317	100,0

**Figure 2. Distribution of Modified-Morisky Adherence Scale (MMAS) in terms of motivation in patient using phosphorus-binding drugs**

MMAS	Number	%
0	7	2,2
1	93	29,3
2	129	40,7
3	88	27,8
4	317	100

While the mean phosphorus level of 100 (31.5%) patients with low MMAS scores was  $5.8 \pm 1.3$  mg/dl, the mean phosphorus level of 217 (68.5%) patients with high scores was  $5.1 \pm 1.2$  mg/dl, and the difference between them was statistically highly significant ( $p=0.001$ )

Although the mean phosphorus level of 96 (20.5%) patients aged 65 and over using phosphorus-binding drugs was  $4.9 \pm 1.2$  mg/dl, the mean value was  $5.5 \pm 1.3$  mg/dl in 221 patients under 65 years of age, and the difference between them was statistically significant ( $p=0.002$ ).

There was no statistically significant difference between the groups when the phosphorus level of the patients using phosphorus-binding drugs, in terms of gender, living alone or with a family, marital status monthly income, educational status, diabetes or not ( $p>0.05$ ). While the mean serum phosphorus level of 37 (11.7%) smokers was  $5.8 \pm 1.4$  mg/dl, the mean phosphorus level of 280 (88.3%) non-smokers was  $5.3 \pm 1.3$  mg/dl, and the difference between them was statistically significant ( $p=0.03$ ).

The mean serum phosphorus level of 139 (43.8%) patients with 9 or less daily tablets was  $5.1 \pm 1.2$ , and the mean phosphorus level of 178 (56.2%) patients who used 10 or more tablets was  $5.5 \pm 1.3$ . The difference between the two groups was statistically significant ( $p=0.009$ ). Among the patients using phosphorus-binding drugs, the mean serum phosphorus level of 141 (44.5%) patients using 5 or more drug types was  $5.3 \pm 1.3$  mg/dl, whereas the mean phosphorus level of 176 (55.5%) patients using less than 5 drug groups was  $5.4 \pm 1.3$  mg/dl. dl and the difference between them was not statistically significant ( $p>0.05$ ).

**Table 2 Distribution of Socio-Demographical Characteristics by Gender**

Socio-Demographic Characteristics	Male		Female	
	Number	%	Number	%
<b>Marital status</b>				
Married	176	85.0	105	68.2
Single	20	9.7	10	6.5
Divorced	11	5.3	39	25.3
<b>Who do you live with</b>				
Alone	4	1.9	5	3.2
Family	203	98.1	149	96.8
<b>Working in income generating job</b>				
Yes	27	13.0	3	1.9
No	180	87.0	151	98.1
<b>Educational status</b>				
Illiterate	17	8.2	70	45.5
Primary education	147	71.0	72	46.8
High school	35	16.9	8	5.2
University	8	3.9	4	2.6
<b>Smoking</b>				
Yes	37	17.9	4	2.6
No	170	82.1	150	97.4
<b>Alcohol use</b>				
Yes	5	2.4	0	0.0
No	202	97.6	154	100.0

**Table 3. Distribution of Causes of Chronic Kidney Failure in Patients**

Cause	Patient Nubmer (%)
Hypertension	127(35)
Diabetes Mellitus	98(27)
Unknown	47(13)
Polycystic Kidney Disease	29(8)
Other	24(7)
Glomerulonephritis	23(6)
Amyloidosis	6(2)
Obstructive Nephropathy	7(2)
<b>Total</b>	<b>361 (100)</b>

**Table 4. Distribution of patients according to the number of drug groups used daily**

Number of drug groups per day	Number of patients ( %)
1	3(0.8)
2	40(11.1)
3	81(22.4)
4	83(23.0)
5	82(22.7)
6	51(14.1)
7	16(4.4)
8	5(1.4)
<b>Total</b>	<b>361 (100)</b>

**Table 5 Distribution of the patients according to the number of drug tablets used daily**

Number of medication tablets per day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	22	25	Total
Number of patients	4	7	14	12	25	28	52	34	36	30	35	35	12	8	10	5	9	2	1	1	1	<b>361</b>
%	1.1	1.9	3.9	3.3	6.9	7.8	14.4	9.4	10	8.3	9.7	9.7	3.3	2.2	2.8	1.4	2.5	0.6	0.3	0.3	0.3	<b>100</b>

## Discussion

Polypharmacy is an increasing problem day by day because chronic diseases require long-term drug therapy and is associated with high morbidity and mortality (7). Polypharmacy complicates treatment, reduces adherence to treatment, increases costs and poses a problem for health-social security systems.

Polypharmacy is an increasing problem with the emergence of new supportive therapies in hemodialysis patients. Although polypharmacy is common in hemodialysis patients, the main problem in this patient group is the high tablet load. Considering the existence of drugs that need to be taken 6-9 tablets a day, especially phosphorus binders, the excess drug load of dialysis patients can be better understood.

Adherence with treatment regimens, as well as polypharmacy, remains a challenge for chronic dialysis patients and their medical caregivers. Poor adherence of the patient to the treatment may adversely affect the treatment results (5).

Chronic dialysis patients have to receive an average of 6-10 different treatments per day. These patients often receive a complex treatment regimen that includes phosphorus binders, vitamin D or calcimimetic preparations, statin agents, antihypertensive treatments, hypoglycemic agents, erythropoietin and iron supplements, and additional treatments for comorbidity (8). An important point in the non-adherence of hemodialysis patients is that it varies according to the drug class (9). The increase in serum phosphorus level is an independent risk factor for the development of bone mineral disease and mortality in patients with chronic renal failure or undergoing dialysis due to end-stage renal failure. There are several important methods in the treatment of hyperphosphatemia, which has such a negative effect on mortality. These; regulation of the diet, the use of phosphorus-binding drugs, and the application of effective and adequate dialysis (10).

In previous studies, they gave more importance to factors such as diet, fluid restriction and participation in dialysis in terms of determinants of adherence to treatment in hemodialysis patients. (11,12). Recently, however; Due to the large number of drugs required by hemodialysis patients on a daily basis, noncompliance due to not taking the drug directly or taking it irregularly is thought to be an important problem for this population. (13).

In 3 different studies, the average number of drugs taken by hemodialysis patients was found to be 11,10,13 tablets (8,14-15). The daily number of drugs of the patients in our study ranged from 1 to 8, and the average number of drug groups was found to be 5. The number of tablets taken daily was between 2-25, and the average number of tablets taken daily was 10. All these studies show that polypharmacy and especially tablet load pose a serious problem in chronic dialysis patients, which is supported by our study.

In studies, the compliance rate of hemodialysis patients to drug treatments has been reported in a wide range as 22-74% (mean 51%) (16). In studies evaluating the nonadherence of phosphorus-binding drug, the nonadherence rate was found to be 61% by Hartman et al. and 50% in the study by Bame et al (17-18). In our study, the limit of serum phosphorus level was taken as 5.5, and the nonadherence rate was found to be 40.4%.

In our study, the patient's marital status, gender, income level, diabetes or not, treatment compliance differed from other studies (18-20). Due to the difference in economic development, there may be relative differences between the classes of the countries. The middle class of a developed country may correspond to a standard of living close to the upper income level of a developing country. This may cause the results to be inconsistent. Similar results were seen in our study, where educated patient and elderly patients had better compliance with phosphate-binding drug therapy than younger patients, and smokers had worse compliance(8,21-23).

In all of the above studies, serum phosphorus level was taken as a measure of adherence to treatment. However, it may be insufficient to measure compliance with phosphorus binders by looking at the serum phosphorus level alone. Because phosphorus level is also affected by the patient's diet, dialysis adequacy, residual renal function, urine output, comorbid diseases, hormonal status, acid-base disorders, hypercatabolic states and dialysis type (24). Therefore, in this study, we used a self-reported compliance questionnaire in addition to serum phosphorus levels as a measure of adherence to treatment.

In the study of Tomasella et al. investigating compliance with phosphorus-binding therapy in 129 HD and 59 PD patients, they applied both the serum phosphorus level ( $>5.5$ ) and the compliance questionnaire, which included the patients' self-reports. When the serum phosphorus level was taken as a measure of adherence to treatment, non-compliance was observed in 51% of the patients, and when the compliance questionnaire was taken as a criterion, non-compliance was observed in 38% of the patients (25). In our study, when the serum phosphorus level was taken as a measure of adherence, 40.4% of the patients found non-compliance, and when the compliance questionnaire was taken as a criterion, non-compliance was found in 77.3%. When the compliance questionnaire was taken as a criterion, the reason for the higher rate in our study may be that the questionnaire was conducted in the form of a question and answer interview with the patient, because in the other study, the compliance questionnaire was filled by the patient.

In another study, factors that disrupt compliance in phosphorus-binding therapy were investigated; Forgetfulness, neglect of the treatment, side effects and polypharmacy were found to be the most important causes (26). In our study, there was no difference in terms of non-compliance in those who used 5 or more drugs compared to those who did not. However, when the number of tablets per day was examined, it was seen that the compliance with the drug decreased with the increase in the number of tablets. When the causes of non-compliance were examined, similar results were obtained in our study. While forgetfulness was the most common cause of non-compliance, it was followed by drug side effects and boredom from using drugs.

In our study, according to the MMAS, the serum phosphorus level of the patients who were found to be high in compliance was significantly lower than those of the patients who were found to be inconsistent. This is proof that the MMAS is a good indicator to measure treatment compliance.

The results of the study show that; In order to increase adherence to treatment, all healthcare professionals, especially doctors, should provide more comprehensive education to patients, and patients with low understanding should be given a chart describing the use of the drug. There is no single strategy to increase medication adherence in hemodialysis patients, and studies suggest that behavioral and educational applied strategies should be combined to improve medication adherence pattern. Various strategies such as patient education, behavioral self-control, social and familial support, and effective patient-doctor communication can facilitate the increase in treatment compliance (27).

### Study Limitation

Our study has some limitations. First, the sample size of the study was relatively small. Second, in this study, hemodialysis patients were relatively heterogeneous in disease duration.

### Conclusion

In conclusion, polypharmacy and non-compliance with phosphorus-binding drugs are common in hemodialysis patients. And we think that more, more advanced and quality research is needed to improve adherence on this subject.

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