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SELF-REPORTED MEDICATION ADHERENCE CORRELATES WITH PHOSPHATE LEVELS, RESIDUAL DIURESIS AND NUTRITIONAL STATUS IN HEMODIALYSIS PATIENTS: AN INTERNATIONAL MULTICENTER STUDY

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Compliance is a major obstacle to achieving phosphorus control in the majority of patients with end-stage renal disease. We investigated self-reported medication adherence and its correlation with serum phosphate levels and nutritional status in hemodialysis patients. A total of 417 patients from Croatia, Montenegro and Bosnia and Herzegovina, mean age 63.82 (range, 21-92) years, were included in the study. There were 55.1% of male patients with the mean dialysis vintage of 68.67 (range, 3-456) months. A significant positive correlation was found between self-reported adherence and serum phosphorus (0.192), and negative correlation with hemoglobin, prealbumin, albumin, Kt/V and residual diuresis (-0.187, -0.227, -0.100, 0.192, and -0.106, respectively). On the other hand, the number of pills taken daily correlated significantly with residual diuresis, serum prealbumin, serum glucose, triglycerides, ferritin and ultrafiltration volume (0.241, 0.154, 0.158, 0.112, 0.201 and 0.125, respectively). In conclusion, self-reported medication adherence correlates with serum phosphate levels, residual diuresis and nutritional status in hemodialysis patients.

Key words: medication adherence, phosphate level, nutritional status, pill burden

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INTRODUCTION

Hemodialysis patients have numerous limitations and require multiple drugs to correct abnormalities associated with chronic kidney disease (CKD). Accumulation of phosphorus is an important problem in this population, which affects morbidity and mortality (1). Lowering the phosphate load and maintaining serum phosphorus levels within the normal range are considered important therapeutic goals to improve clinical outcomes in CKD patients. Treatment consists of diminishing intestinal phosphate absorption by a low phosphate diet and phosphate binders, however, their efficacy is often limited by poor adherence (2).

The aim of this multicenter, cross-sectional, observational study was to investigate correlation of self-reported medication adherence with serum phosphate levels and nutritional status in hemodialysis patients.

PATIENTS AND METHODS

Adult subjects receiving dialysis treatment for end-stage renal disease were recruited from three Croatian dialysis centers (Zagreb, 99 patients; Rijeka, 91 patients; and Avitum, 105 patients), one center from Bosnia and Herzegovina (Sarajevo, 73 patients), and one center from Montenegro (Podgorica, 49 patients). Subjects were eligible for participation if they were aged 18 years or older and currently prescribed phosphate binder medication therapy. Exclusion criterion was the existing diagnosis of psychosis or dementia. Demographic information was collected by subject interview, while pill burden was documented after review of medication containers and confirmed by subject interview. Comorbidity and laboratory results were abstracted from medical charts and records. L*aboratory data* were collected for the past three months, and the mean of all measured values over the three-month period was used for analysis. Malnutrition Inflammation Score (MIS) (3) was determined. The self-made modification of Morisky Medication Adherence Scale (MMAS) (4) was used to determine self-reported medication adherence. Each positive answer is scored one point. The scale range is 0-8, with 0 denoting most compliant and 8 least compliant. Surveys were administered to each subject during a face-to-face interview, before dialysis treatment.

The study was conducted according to ethical standards. Informed consent was obtained from all participants included in the study.

Statistical analysis was performed using Stata/SE 11.2 for Windows (StataCorp LP, USA). Differences between two groups were analyzed by Pearson χ^2-test (or Fisher exact test if any expected cell frequency in contingency table was ≤5) for categorical variables, by Student's *t*-test for normally distributed continuous variables, and by Mann Whitney U test for non-normally distributed continuous variables, at the level of significance $p<0.05$. Spearman rank order correlation was used to determine correlation between variables.

RESULTS

The multinational study included 417 prevalent hemodialysis patients. Characteristics of study subjects are presented in Table 1.

Table 1.
Characteristics of the study population

Parameter	Mean (range)
Age (yrs)	63.825 (21-92)
Dialysis vintage (months)	68.674 (3-456)
Body mass index (kg/m^2)	25.66 (16.6-70)
Hemoglobin (g/L)	107.86 (63-142)
Prealbumin (g/L)	0.411 (0.12-0.9)
Albumin (g/L)	38.25 (23.6-41)
Phosphorus (mmol/L)	1.65 (0.37-3.5)
iPTH (pmol/L)	41.42 (0.2-166)
Kt/V	1.31 (0.6-2.5)
Residual diuresis (L)	183.48 (0-4000)
MIS	6.78 (0-17)
No. of pills	7.72 (1-23)
Adherence score	6.33 (0-8)

Data are presented as mean with range and standard deviation; iPTH, intact parathyroid hormone; MIS, malnutrition-inflammation score

Sarajevo and Podgorica had a significantly higher, and Zagreb and Avitum significantly lower Morisky score, whereas Rijeka differed significantly from all other centers (Figure 1).

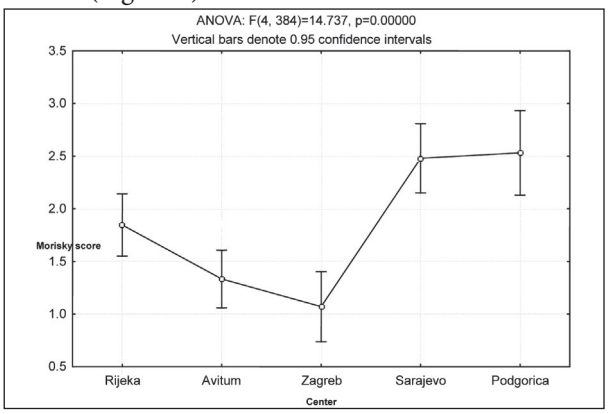

Fig. 1. *Self-reported adherence score in different dialysis centers*

These results were in contrast with the number of prescribed pills (Figure 2) and MIS (Figure 3).

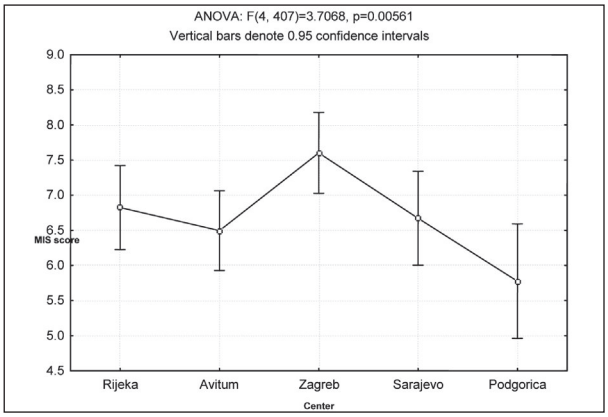

Fig. 2. *Number of pills prescribed in different dialysis centers. Patients from Podgorica had a significantly lower number of pills prescribed per day compared to other centers.*

Significant correlation was found between Morisky score and serum hemoglobin, prealbumin, albumin, phosphorus, Kt/V and residual diuresis. On the other hand, pill load (number of pills) correlated significantly with residual diuresis, serum prealbumin, serum glucose, triglycerides, ferritin, and ultrafiltration volume (Table 2).

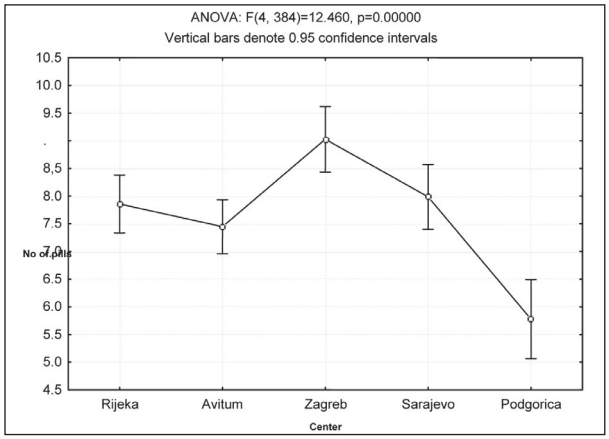

Fig. 1. *Malnutrition Inflammation Score*

Table 2.
Spearman rank order correlations

Variable	No. of pills	Morisky score
Correlation coefficient		
Age (yrs)	-0.071477	-0.091643
Dialysis vintage (months)	0.012715	-0.084853
BMI (kg/m^2)	0.046584	0.013244
UF volume (L)	0.125004#	-0.027500
Hemoglobin (g/L)	0.043909	-0.187647#
Ferritin (ug/L)	0.201665#	-0.063710
C-reactive protein (mg/L)	0.039986	-0.031973
Creatinine (umol/L)	-0.072086	0.075605
Glucose (mmol/L)	0.158771#	-0.061612
Bicarbonates (mmol/L)	-0.010552	0.004451
Prealbumin (g/L)	0.154281#	-0.227937#
Albumin (g/L)	0.048469	-0.100130#
Cholesterol (mmol/L)	0.020321	0.066326
Triglycerides (mmol/L)	0.112518#	0.053302
Magnesium (mmol/L)	-0.035197	0.097824
Calcium (mmol/L)	0.014945	0.017921
Phosphorus (mmol/L)	-0.058356	0.192388#
iPTH (pmol/L)	0.050372	0.074018
Kt/V	0.091101	-0.106728#
Residual diuresis (L)	0.241750#	-0.119067#
MIS	0.044434	-0.065495

#correlation significant at p<0.05; BMI, body mass index; iPTH, intact parathyroid hormone; MIS, malnutrition-inflammation score

Patients with phosphate levels within the target range had a significantly lower Morisky score (better compliance) than patients with increased phosphate levels (Figure 4). There was no difference either between patients with iPTH within the target range (less than 9-fold normal level) and patients with higher values, or between those with hemoglobin between 100 and 120 g/L and those with lower hemoglobin values.

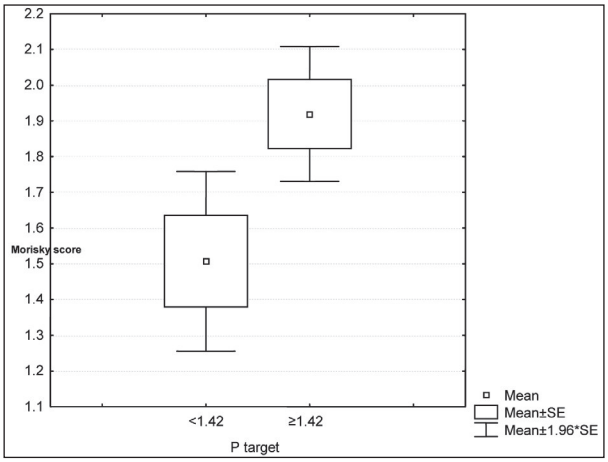

Fig. 4. *Patients with serum phosphate levels within the target values had a significantly lower Morisky score compared to patients with higher phosphate levels.*

DISCUSSION

Study results demonstrated significant relationship between the self-reported medication adherence and serum phosphate levels. Patients with lower adherence determined by the Morisky score had higher serum phosphate levels. According to our results, the number of daily ingested pills correlated significantly with residual diuresis, serum prealbumin, serum glucose, triglycerides, ferritin and ultrafiltration volume, but not with the self-reported medication adherence. Significant differences were recorded between dialysis centers from Croatia (Zagreb, Rijeka, and Avitum) and those from Bosnia and Herzegovina and Montenegro. The main reason for these differences may be the long-standing practice of individual patient education in Croatian dialysis centers, which starts at the predialysis stage and continues during dialysis treatment with emphasis on nutrition and use of phosphate binders based on phosphorus content in each meal. Thus, demographic parameters strongly influenced the results.

Maintenance of phosphorus control in dialysis patients is based on nutritional advice to balance phosphate content of the diet with the use of oral phosphate binders. The majority of binders were studied using the traditional breakfast, lunch and dinner meal model. However, the majority of dialysis patients eat either more small frequent meals and snacks, which may decrease the effectiveness of the binders, or only one or two meals *per* day. Adherence to phosphate binder

use as prescribed was estimated to be less than 50% (5,6). Individual approach is mandatory because patients differ significantly according to age, health literacy, cognitive function, and adherence. It is up to the dialysis medical team to keep patients interested with consistent and creative communication.

To the best of our knowledge, we demonstrated correlation between the parameters of nutritional status (prealbumin and albumin) with self-reported medication adherence for the first time. This may be an important finding revealing that excellent results may be achieved with a more liberal diet in patients compliant with the use of phosphate binders. These findings are in line with previous findings demonstrating the most favorable outcomes in patients with high protein intake and good phosphate control (7). Correlation of Morisky score with residual diuresis may be an additional important finding, showing that compliant patients may preserve residual renal function.

There were several limitations to this study. First, the cross-sectional study design made it difficult to determine temporal sequencing. Second, our sample size was small. Finally, we used a self-reported measure of phosphate binder adherence, which is subject to recall and information bias (although validated) (4).

In conclusion, self-reported medication adherence significantly correlated with serum phosphate levels, residual diuresis and nutritional status in dialysis patients. Significant differences existed among dialysis centers, with better results achieved in the centers with structured predialysis and dialysis education.

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SAŽETAK

SAMOPROCIJENJENA SURADLJIVOST BOLESNIKA KORELIRA SA SERUMSKIM FOSFOROM, OSTATNOM DIUREZOM I STATUSOM UHRANJENOSTI BOLESNIKA NA HEMODIJALIZI: MEĐUNARODNO, MULTICENTRIČNO ISTRAŽIVANJE

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Suradljivost je glavna prepreka kontroli fosfora u većine bolesnika sa završnim stadijem kronične bubrežne bolesti. Istražili smo povezanost suradljivosti s uzimanjem lijekova, procijenjene od strane samih bolesnika, s koncentracijom fosfora u serumu i statusom uhranjenosti bolesnika na hemodijalizi. U istraživanje je uključeno 417 bolesnika iz Hrvatske, Crne Gore i Bosne i Hercegovine. Prosječna dob bila je 63,82 godine (raspon, 21-92), 55,1 % ih je bilo muškog spola, prosječno liječenih dijalizom 68,67 (raspon, 3-456) mjeseci. Nađena je statistički značajna pozitivna korelacija između suradljivosti i serumskog fosfora (0,192), a negativna s prealbuminom, albuminom, Kt/V i ostatnom diurezom (redom, -0,187, -0,227, -0,100, 0,192 i -0,106). S druge strane, broj dnevno unesenih tableta je statistički značajno korelirao s ostatnom diurezom, serumskim prealbuminom, glukozom, trigliceridima, feritinom i volumenom ultrafiltracije (redom, 0,241, 0,154, 0,158, 0,112, 0,201 i 0,125). Zaključno, samoprocijenjena suradljivost bolesnika korelira sa serumskim fosforom, ostatnom diurezom i statusom uhranjenosti bolesnika na hemodijalizi.

Ključne riječi: suradljivost, fosfor, status uhranjenosti, količina lijekova