Nephrol Dial Transplant (2014) 29: 2092–2099
doi: 10.1093/ndt/gft280
Advance Access publication 5 September 2013

Serum phosphorus levels and pill burden are inversely associated with adherence in patients on hemodialysis

Steven Wang[1], Thomas Alfieri[1], Karthik Ramakrishnan[1], Peter Braunhofer[2] and Britt A. Newsome[3]

[1]DaVita Clinical Research, Minneapolis, MN, USA, [2]Vifor Fresenius Medical Care Renal Pharma, Glattbrugg, Switzerland and [3]Denver Nephrology, Denver, CO, USA

Correspondence and offprint requests to: Steven Wang; E-mail: steven.wang@davita.com; journalsubmission@davita.com

ORIGINAL ARTICLE

ABSTRACT

Background. Phosphate binders (PBs) account for about one half of the daily pill burden for US hemodialysis (HD) patients, which may reduce adherence. Adherence can be estimated by the medication possession ratio (MPR), which is defined as the proportion of time a patient had sufficient medication to have taken it as prescribed. Gaps of time between prescription fills lower the patient's MPR. We assessed the association of PB pill burden and adherence (MPR) with phosphorus goal attainment.

Methods. Using pharmacy management program data, HD patients on PB monotherapy were tracked from first PB fill during 1 January 2007–30 June 2011 for 1 year, or until PB change or censoring. Data were assessed with generalized linear models.

Results. We analyzed 8616 patients. Higher pill burden was associated with lower adherence. Lower adherence tended to be associated with higher mean phosphorus levels and lower percentage of patients with serum phosphorus ≤5.5 mg/dL ($P < 0.001$). The association between adherence and these clinical outcomes was most pronounced in the lowest and highest pill burden strata (<3, >3–6, >12–15, >15).

Conclusions. Adherence, as measured by the MPR, was negatively related to higher pill burden and phosphorus levels and positively related to patients in the phosphorus target range. Within pill burden strata, phosphorus increased and patients in the target range generally decreased with decreasing adherence, suggesting that patients prescribed fewer PB pills are less likely to have treatment gaps, and may be more likely to achieve phosphorus targets.

Keywords: adherence, hemodialysis, phosphate binders, pill burden, retrospective study

INTRODUCTION

Among hemodialysis (HD) patients, bone and mineral metabolism dysregulation is a serious and pervasive problem [1, 2]. Markers of mineral and bone disorders (MBD), including hyperphosphatemia, secondary hyperparathyroidism and hypercalcemia, have been associated with increased risk of hospitalization and mortality [3–10]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) specifies that serum phosphorus levels should be maintained between 3.5 and 5.5 mg/dL, primarily through dietary restrictions and phosphate binders (PBs), yet only 41–64% of dialysis patients are able to maintain phosphorus within the target range [11, 12]. Similarly, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for bone and mineral disorders suggest lowering elevated phosphorus levels toward the normal range, although no specific target range is prescribed [13].

PB nonadherence may complicate serum phosphorus control [2, 14]; on average, over half of dialysis patients are not adherent to their PB regimes, but this level ranges from 21 to 74% depending on the patient population and measurement method [2, 15–21]. Adherence may be affected by pill burden. PBs often pose a large pill burden [14], accounting for nearly half of the high daily total pill burden (median, 19) for US HD patients [22]. Higher pill burden is associated with lower health-related quality of life [22].

Measuring the impact of treatment adherence on patient outcomes is difficult, in large part due to the challenges of quantifying 'adherence.' The medication possession ratio (MPR) is an effective way to estimate adherence. The MPR is the proportion of days the patient had sufficient medication available to have taken the medication as prescribed. It is calculated from the number of days' worth of medication supplied to the patient within a refill interval in relation to the number of days in the refill interval [23, 24]. Long gaps of time between medication refills will lower a patient's MPR.

We hypothesized that lower PB pill burden would be associated with higher treatment adherence and more favorable clinical outcomes (such as low serum phosphorus levels and more frequent attainment of KDOQI phosphorus goals). To test this hypothesis, we evaluated the association of PB pill burden with adherence (measured by MPR), serum phosphorus levels and time in recommended phosphorus range by conducting a retrospective, observational study of a large dialysis provider's electronic medical records and pharmacy management program.

SUBJECTS AND METHODS

Study design

In this retrospective, observational study, we examined PB pill burden, adherence and serum phosphorus levels among prevalent HD patients on PB monotherapy receiving care at a large dialysis organization (LDO) and participating in a pharmacy management program between 1 January 2007 and 30 June 2011. The program was a full-service pharmacy that delivered prescriptions and over-the-counter medications directly to the patient's dialysis facility or their home. The program provided medication review by pharmacists upon enrollment, weekly refill reminders, assistance with pre-authorization services and individualized payment plans. Patients enrolled in the program could fill their prescription at a local pharmacy if needed. Patients could enroll in a refill management system (RMS) within the program, allowing patients to have prescriptions refilled automatically when they were expected to run out.

Patients in the study were ≥18 years old, receiving in-center HD three times or more per week, Medicare patients receiving care in the LDO's facilities during the time frame and continuously enrolled in the pharmacy management program with no gap >180 days between prescription fills. Patients were excluded if they were receiving peritoneal dialysis, home HD or nocturnal HD; were enrolled in the pharmacy management RMS program for PBs; were receiving the powder or sachet formulation of sevelamer; or had serum phosphorus levels <3.0 mg/dL.

Patients were tracked from first PB prescription fill during the specified period for 1 year or until a censoring event. Patients were censored if they switched PB type, received prescriptions for multiple PBs, enrolled in the automatic RMS, had a gap of 180 days between fills of all medications in the pharmacy management program, had two consecutive serum phosphorus levels <3.0 mg/dL, discontinued HD or died. Patients with two consecutive serum phosphorus levels <3.0 mg/dL were censored because these patients are often considered to have hypophosphatemia, tend to be different from the general population and are usually taken off PBs.

Medication possession ratio

The MPR reflects the proportion of time a patient had sufficient medication supply available to take the medication as prescribed. For a patient to be in compliance with prescriptions, they must—at a minimum—have filled the prescriptions and, therefore, have the pills in their possession. An MPR of <1.0 indicates that the patient did not have enough medication to take as prescribed. The MPR was calculated starting with the first prescription fill and for a maximum of 1 year or until a censoring event. The MPR was defined as follows:

$$\text{MPR} = \frac{\text{Days Supplied in Period} \; - \; \text{Excess Days}}{\text{Days in Period (patient-time method) OR Days Covered by Orders in Period (order method)}}$$

'Days Supplied in Period' was the total number of days' worth of medicine covered by a given prescription fill. On occasion, patients refilled their prescription before their current medication supply was exhausted, resulting in the patient having extra medication. To account for this, 'excess days' was defined as the number of days' worth of medication left over at the end of the previous prescription period, and was subtracted from the total number of days' worth of medicine covered in the current period. 'Days in Period' was the total days in the observation period. Thus, in the patient-time method, the numerator was equal to the number of days with medication available, and the denominator was equal to the number of days the patient was in the study. The patient-time method is the traditional manner of defining the MPR. Because we had access to prescription information through the pharmacy management database, we also calculated the MPR using a second method, the order method, which explicitly included prescription orders information in calculating the total number of days a patient was prescribed medication. For the order method, 'Days Supplied in Period' and 'Excess Days' are defined the same as for the patient-time method. The 'Days Covered by Orders in Period' was the number of days covered by an order in the pharmacy management database. The denominator in the order method formula was often equal to that of the patient-time method, but could be smaller if there was a gap in prescriptions. Given that the order method MPR draws upon this additional information and does not rely upon the assumption that the patients' prescriptions are continuous, the order method MPR may be a more accurate reflection of compliance, although both methods use the same fundamental calculation.

Definitions

The mean phosphorus level was defined as the average of per-patient mean values for all tests over the period. The percentage of patients with a phosphorus concentration of ≤5.5 mg/dL, defined as 'in–range,' was calculated as the percentage of patients with an overall mean phosphorus concentration of ≤5.5 mg/dL after censoring. Phosphorus means were weighted by the amount of patient-time in days contributed by each patient to account for the number of days each patient was included in the analysis. Pill burden was defined as the mean number of pills/day for days covered by a pharmacy management program prescription. The MPR was defined as the percentage of days during which the patient had pills available to take, using either the order or patient-time method. Definitions of pill burden and MPR strata were based on an initial view of the distribution of the data.

Statistical analysis

Outcome variables were mean MPR, mean phosphorus level and percentage of patients in the phosphorus range (≤5.5 mg/dL). The mean MPR was stratified by pill burden. The mean phosphorus level and percentage of patients in the phosphorus range were stratified by pill burden and also by the MPR. Generalized linear models (GLMs) were used to determine associations between strata (categorical) and outcome variables using SAS version 9.2.

RESULTS

Patient characteristics

Prevalent HD patients on PB monotherapy who were enrolled in the pharmacy management program were evaluated for pill burden, phosphorus levels and adherence. Patients included in the analysis received sevelamer, calcium acetate or lanthanum chloride (Supplementary Data Table S1). Because this analysis focused specifically on pill burden, patients receiving the sachet or powder form of sevelamer were excluded. Twenty-eight percent of patients that switched PB therapy or received dual therapy were also excluded. Adherence was assessed using MPR via two independent methods, the order method and the patient-time method. For the patient-time method, 9346 patients who met all inclusion criteria were included in the analysis, and the MPR was assessed based on the total number of days the patient was included in the study. For the order method, the MPR was calculated based on the number of days for which patients had a physician order for PB therapy: 8616 patients with available order information were included; 730 patients were excluded from this analysis due to missing order information (Table 1). Patient demographics for the 730 patients who were excluded due to missing order information were not systematically different from the demographics for the patients analyzed.

Table 1. Patient demographics for order method analysis

	Total *n*	Mean ± SD
Total *n*	8616	
Age (years)		57.0 ± 14.3
Vintage (years)		3.8 ± 3.6
	n	Percent
Gender (% males)	4518	52.4%
Race/ethnicity		
White	1940	22.5%
Black	3875	45.0%
Hispanic	2199	25.5%
Asian	253	2.9%
American Indian or Alaskan Native	64	0.7%
Native Hawaiian or Pacific Islander	87	1.0%
Primary cause of ESRD		
Diabetic kidney disease	3795	44.1%
Hypertensive kidney disease	2782	32.3%
Other/unknown	1847	21.4%
Polycystic kidney disease	192	2.2%

Pill burden, medication possession ratio and serum phosphorus calculated by the order method

The MPR calculated using the order method includes both proportion of time the patient had doctor's orders to take the medication and medication to take based on the data from the pharmacy management program database. Overall, the mean weighted MPR levels were low, ranging from 51% in the group with the lowest pill burden (0–3 pills/day) to 42% in the group with the highest pill burden (>15 pills/day). The MPR was negatively associated with pill burden ($P < 0.001$; Figure 1A, Table 2). The MPR was also negatively associated with mean phosphorus levels ($P < 0.001$; Figure 1B, Supplementary Figure S1).

The negative relationship between the MPR and mean phosphorus levels was also examined within pill burden strata. Within most pill burden strata (0–3, >3–6, >12–15 and >15 pills/day), a lower MPR was associated with a higher mean phosphorus level. However, a non-linear pattern emerged within the >6–9 and >9–12 pills/day strata ($P < 0.001$ using GLM; Figure 1C, Table 2) with the lowest MPR associated with the highest mean phosphorus concentration, but the middle range MPR associated with the lowest mean phosphorus concentration. Similarly, when the percentage of patients with a mean phosphorus concentration of ≤5.5 mg/dL was assessed by pill burden strata, a higher MPR was associated with a higher percentage of patients with a serum phosphorus concentration of ≤5.5 mg/dL within each pill burden stratum. The difference was significant among strata ($P < 0.001$ using GLM analysis; Figure 1D, Table 2). In the 6–9 and 9–12 pills/day strata, a non-linear pattern was again noted with the lowest MPR associated with the lowest percentage of patients with a serum phosphorus concentration of ≤5.5 mg/dL, while the middle range MPR was associated with the highest percentage of patients with a serum phosphorus concentration of ≤5.5 mg/dL.

Pill burden, medication possession ratio and serum phosphorus calculated by the patient-time method

The MPR was also calculated using the more traditional patient-time method, in which the numerator was defined as the days with medication available, and the denominator was defined as the number of days the patient was in the study and relies on the assumption that the patients' prescriptions are continuous throughout the analysis. Using the patient-time method, the MPR was negatively associated with pill burden, 48% in the lowest pill stratum to 40% in the highest pill stratum ($P < 0.001$; Figure 2A, Table 3). The MPR was negatively associated with serum phosphorus levels ($P < 0.001$; Figure 2B, Table 3) with a serum phosphorus concentration of 5.59 mg/dL within the 0 to ≤0.4 MPR strata; 5.44 mg/dL within the >0.4 to ≤0.6 MPR stratum; 5.37 mg/dL within the >0.6 to ≤1.0 MPR stratum. As with the order method, higher mean phosphorus levels were associated with a lower MPR in general and showed a U-shaped pattern at 6–9 and 9–12 pills/day when stratified by MPR. The difference in mean phosphorus concentration by both pill burden and MPR strata was significant among strata ($P < 0.001$ using GLM analysis;

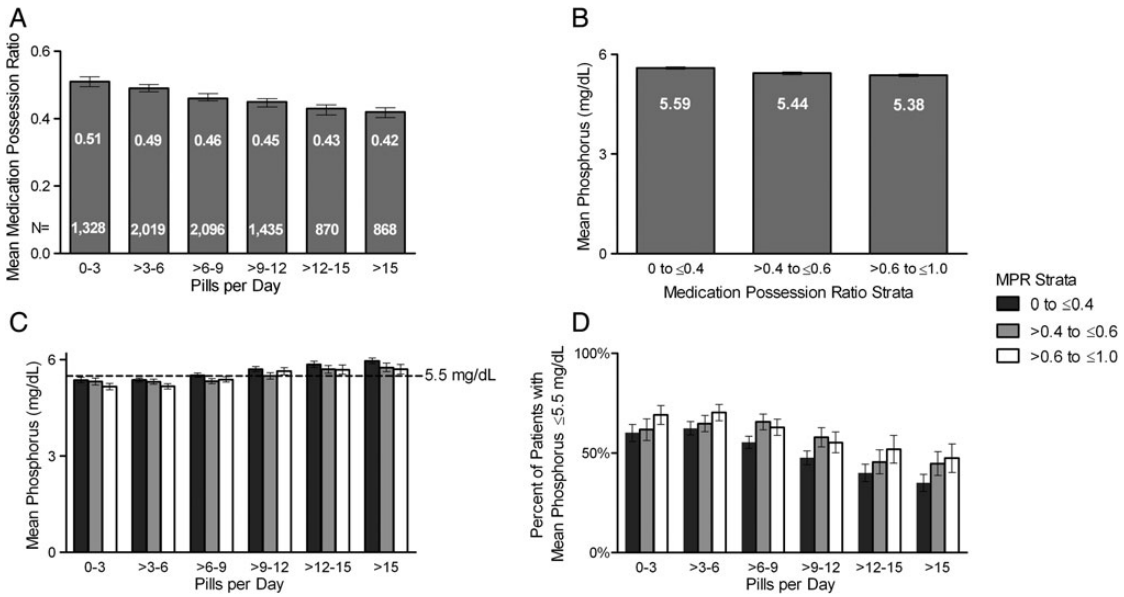

FIGURE 1: Pill burden, MPR and serum phosphorus calculated using the order method. (**A**) Weighted MPR by pill burden using the order method. The MPR was calculated as the days supplied in the period minus the excess days divided by the days covered by orders in the period. The mean MPR for each stratum is shown; $P < 0.001$ among strata by GLM; total $n = 8616$. Sample sizes for each pill burden stratum are shown at the base of the column. Error bars represent 95% confidence intervals (CIs). (**B**) Mean Phosphorus Levels Stratified by MPR using Order Method. Mean phosphorus concentration was calculated as the mean of per patient values for all tests of the period. Phosphorus means were weighted by the amount of patient–time contributed by each patient; $P < 0.001$ among strata by GLM; total $n = 8616$. Error bars represent 95% CIs. (**C**) Mean phosphorus by pill burden and MPR strata using the order method. Mean phosphorus was calculated as the mean of per patient values for all tests of the period. Phosphorus means were weighted by the amount of patient-time contributed by each patient. Lower MPR was associated with a higher mean phosphorus level ($P < 0.001$ among strata using GLM); a non-linear pattern emerged within the >6–9 and >9–12 pills/day strata. Error bars represent 95% CIs. (**D**) Percentage of patients with mean serum phosphorus ≤5.5 mg/dL by Pill Burden and MPR strata using the order method. The percentage of patients with phosphorus ≤5.5 mg/dL was calculated as the percentage of patients with an overall mean phosphorus of ≤5.5 mg/dL within the research period after censoring; total $n = 8616$. Higher MPR was positively associated with a higher percentage of patients with a serum phosphorus concentration of ≤5.5 mg/dL within each pill burden stratum (the difference was significant among strata, $P < 0.001$ using GLM analysis); in the >6–9 and >9–12 pills/day strata, a non-linear pattern was noted. Error bars represent 95% CIs.

Table 2. Pill burden, MPR and serum phosphorus calculated using the order method

Pills per day	Mean MPR (95% CI)	MPR stratum	Mean phosphorus, mg/dL (95% CI)	Percent of patients with phosphorus ≤5.5 mg/mL (95% CI)
0 to <3	0.509 (0.495, 0.524)	0.0 to ≤0.4	5.361 (5.271, 5.451)	60.1 (55.8, 64.4)
		>0.4 to ≤0.6	5.320 (5.207, 5.433)	61.7 (56.3, 61.1)
		>0.6 to ≤1.0	5.161 (5.062, 5.259)	69.1 (64.4, 73.8)
3 to <6	0.490 (0.479, 0.501)	0.0 to ≤0.4	5.366 (5.298, 5.434)	62.4 (59.2, 65.7)
		>0.4 to ≤0.6	5.312 (5.227, 5.397)	64.7 (60.6, 68.7)
		>0.6 to ≤1.0	5.166 (5.082, 5.250)	70.3 (66.3, 74.2)
6 to <9	0.463 (0.453, 0.474)	0.0 to ≤0.4	5.515 (5.451, 5.579)	55.4 (52.3, 58.4)
		>0.4 to ≤0.6	5.331 (5.249, 5.414)	65.6 (61.6, 69.5)
		>0.6 to ≤1.0	5.384 (5.298, 5.471)	62.3 (58.9, 67.0)
9 to <12	0.446 (0.434, 0.459)	0.0 to ≤0.4	5.703 (5.628, 5.777)	47.6 (44.1, 51.1)
		>0.4 to ≤0.6	5.489 (5.390, 5.588)	57.9 (53.1, 62.6)
		>0.6 to ≤1.0	5.641 (5.532, 5.751)	55.3 (50.2, 60.5)
12 to <15	0.426 (0.410, 0.441)	0.0 to ≤0.4	5.855 (5.764, 5.946)	40.0 (35.7, 44.4)
		>0.4 to ≤0.6	5.698 (5.572, 5.824)	45.5 (39.5, 51.5)
		>0.6 to ≤1.0	5.685 (5.536, 5.833)	51.9 (44.9, 58.9)
>15	0.418 (0.403, 0.432)	0.0 to ≤0.4	5.965 (5.875, 6.055)	35.0 (30.7, 39.3)
		>0.4 to ≤0.6	5.753 (5.628, 5.878)	44.7 (38.7, 50.7)
		>0.6 to ≤1.0	5.702 (5.550, 5.854)	47.4 (40.2, 54.6)

CI, confidence intervals; MPR, medication possession ratio.

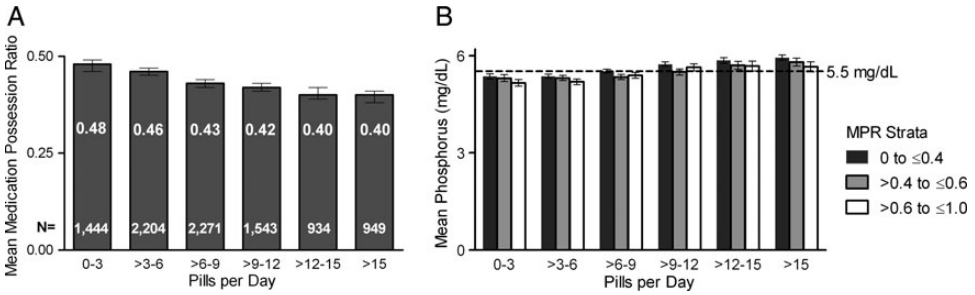

FIGURE 2: Weighted MPR by pill burden and mean phosphorus by pill burden and MPR strata using the patient-time method. (**A**) MPR was calculated as the days supplied in the period minus the excess days divided by the days in the period. Mean MPR for each stratum is shown; P < 0.001 among strata by GLM. Error bars represent 95% CIs. (**B**) Mean phosphorus was calculated as the mean of per patient values for all tests of the period. Phosphorus means were weighted by the amount of patient-time contributed by each patient; total *n* = 9346. Lower MPRwas associated with a higher mean phosphorus level (P < 0.001 among strata using GLM); a non-linear pattern emerged within the >6–9 and >9–12 pills/day strata. Error bars represent 95% CIs.

Table 3. Pill burden, MPR and serum phosphorus calculated using the patient-time method

Pills per day	Mean MPR (95% CI)	MPR stratum	Mean phosphorus (95% CI), mg/dL
0 to <3	0.477 (0.463, 0.490)	0.0 to ≤0.4	5.363 (5.283, 5.442)
		>0.4 to ≤0.6	5.305 (5.198, 5.411)
		>0.6 to ≤1.0	5.159 (5.061, 5.256)
3 to <6	0.461 (0.451, 0.471)	0.0 to ≤0.4	5.364 (5.303, 5.426)
		>0.4 to ≤0.6	5.310 (5.230, 5.391)
		>0.6 to ≤1.0	5.186 (5.102, 5.270)
6 to <9	0.433 (0.424, 0.443)	0.0 to ≤0.4	5.524 (5.467, 5.582)
		>0.4 to ≤0.6	5.339 (5.261, 5.417)
		>0.6 to ≤1.0	5.392 (5.304, 5.480)
9 to <12	0.422 (0.411, 0.434)	0.0 to ≤0.4	5.739 (5.671, 5.806)
		>0.4 to ≤0.6	5.500 (5.404, 5.595)
		>0.6 to ≤1.0	5.637 (5.528, 5.747)
12 to <15	0.405 (0.390, 0.417)	0.0 to ≤0.4	5.854 (5.770, 5.939)
		>0.4 to ≤0.6	5.697 (5.572, 5.822)
		>0.6 to ≤1.0	5.679 (5.529, 5.828)
>15	0.397 (0.384, 0.411)	0.0 to ≤0.4	5.941 (5.858, 6.024)
		>0.4 to ≤0.6	5.799 (5.677, 5.919)
		>0.6 to ≤1.0	5.659 (5.504, 5.814)

CI, confidence intervals; MPR, medication possession ratio

Figure 2B). Thus, in the same population, the associations found in the patient-time method MPR analysis confirm the associations noted in the order method MPR analysis.

Pill burden, medication possession ratio and serum phosphorus for patients enrolled in the automatic refill management system (RMS) calculated by the order method

A portion of patients in the pharmacy management program were enrolled in the RMS and had their prescriptions refilled automatically, or received reminders that the time had come to refill their prescription. RMS patients were excluded from the primary analyses because the RMS may have closed the gaps in medication need, and thus, produced artificially high MPR levels. However, in a separate analysis using the order method, the MPR was calculated for this patient population and was indeed found to be significantly higher than that seen in non-RMS patients (a third of RMS patients had an MPR of >0.90). For the RMS patients, the MPR was still found to be negatively associated with pill burden, with patients in the lowest pill burden stratum having a mean MPR of 0.75 and those in the highest pill burden stratum having a mean MPR of 0.69 (P < 0.001; Figure 3A, Table 4). The MPR was also negatively associated with mean phosphorus levels (P < 0.001; Figure 3B, Table 4).

DISCUSSION

PBs pose a high pill burden to patients. Using data from the pharmacy management program, we assessed the association between pill burden and adherence as measured by the MPR and the association of MPR with phosphorus levels and time in KDOQI target range. MPR levels ranged from 40 to 50%; these low rates are consistent with real-world medication adherence. As expected, a higher pill burden was associated with a lower MPR. Because a lower MPR signifies a longer gap between fills, these data suggest that the patients who are

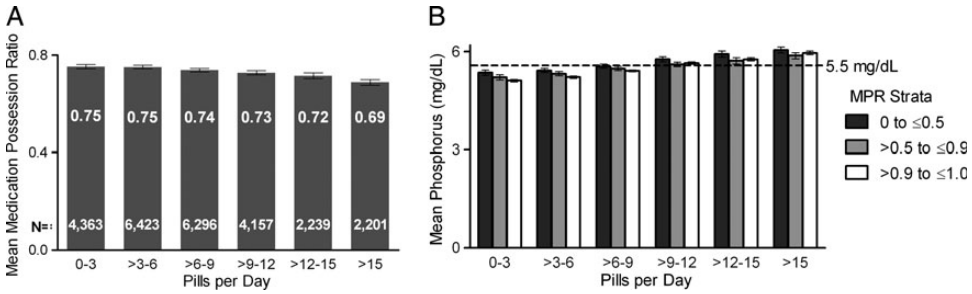

FIGURE 3: Weighted MPR by pill burden and mean phosphorus by pill burden and MPR strata using the order method in patients using the RMS. (**A**) MPR was calculated as the days supplied in the period minus the excess days divided by the days covered by orders in the period. Mean MPR for each stratum is shown; $P < 0.001$ among strata by GLM. Error bars represent 95% CIs. (**B**) Mean phosphorus was calculated as the mean of per patient values for all tests of the period. Phosphorus means were weighted by the amount of patient-time contributed by each patient; total $n = 26\,279$. Lower MPR was associated with a higher mean phosphorus level ($P < 0.001$ among strata using GLM); a non-linear pattern emerged within the >9–12, >12–15 and >15 pills/day strata. Error bars represent 95% CIs.

Table 4. Pill burden, MPR and serum phosphorus calculated using the order method in patients using the RMS

Pills per day	Mean MPR (95% CI)	MPR stratum	Mean phosphorus (95% CI), mg/dL
0 to <3	0.752 (0.744, 0.761)	0.0 to ≤0.5	5.356 (5.275, 5.436)
		>0.5 to ≤0.9	5.212 (5.133, 5.292)
		>0.9 to ≤1.0	5.108 (5.070, 5.145)
3 to <6	0.751 (0.745, 0.758)	0.0 to ≤0.5	5.424 (5.359, 5.489)
		>0.5 to ≤0.9	5.322 (5.259, 5.386)
		>0.9 to ≤1.0	5.215 (5.184, 5.246)
6 to <9	0.738 (0.731, 0.745)	0.0 to ≤0.5	5.554 (5.492, 5.618)
		>0.5 to ≤0.9	5.483 (5.420, 5.546)
		>0.9 to ≤1.0	5.408 (5.377, 5.438)
9 to <12	0.727 (0.719, 0.736)	0.0 to ≤0.5	5.765 (5.691, 5.840)
		>0.5 to ≤0.9	5.610 (5.537, 5.684)
		>0.9 to ≤1.0	5.652 (5.614, 5.690)
12 to <15	0.715 (0.704, 0.727)	0.0 to ≤0.5	5.926 (5.832, 6.021)
		>0.5 to ≤0.9	5.716 (5.616, 5.815)
		>0.9 to ≤1.0	5.764 (5.713, 5.814)
>15	0.688 (0.676, 0.700)	0.0 to ≤0.5	6.052 (5.960, 6.144)
		>0.5 to ≤0.9	5.876 (5.783, 5.970)
		>0.9 to ≤1.0	5.962 (5.909, 6.016)

CI, confidence intervals; MPR, medication possession ratio.

prescribed more pills as part of their PB regimen are more likely to have worse adherence. It also follows that the lowest MPR occurred in patients in the highest pill burden stratum. In general, higher MPR levels were related to lower mean phosphorus levels and a larger percentage of patients with phosphorus ≤5.5 mg/dL. These associations were observed whether the MPR was assessed with the order method or the patient-time method and, moreover, were also observed in patients enrolled in the automatic RMS.

This is the first study of the magnitude of close to 9000 dialysis patients to demonstrate an association of PB pill burden with phosphorus outcomes via levels of medication adherence. Previous much smaller studies have also shown an inverse relationship between adherence and pill burden and a positive association between phosphorus levels and pill burden [22, 25]. The levels of adherence in this study are similar to previous estimates from a systematic review reporting a mean non-adherence rate of 51% (range 22–74%) [2]. Consistent with our results, Arenas *et al.* found that serum phosphorus levels were significantly higher in nonadherent patients and those patients were at greater risk of being outside target phosphorus range [21]. In the Arenas study, adherence was measured among 165 patients receiving HD at a single dialysis unit using the patient-reported Simplified Medication Adherence Questionnaire. Chiu *et al.* noted a significant, inverse, non-linear relationship between pill burden and adherence with a large increase in nonadherence in patients prescribed >12 pills/day [22]. In that study of 233 prevalent dialysis patients, PB burden was calculated based on pills brought from home by the patient and adherence was calculated as the actual number of pills consumed divided by the expected number of pills consumed from the time of last refill to the study visit date, based on the prescription label of the patient-supplied medication. Adherence and patient satisfaction were shown to improve when pill burden was reduced due to a switch to a higher strength PB [25]. Yet 54% of patients were reported to

be dissatisfied with their prescribed PB and those patients had higher serum phosphorus levels [20]. Thus, serum phosphorus levels are influenced by adherence which, in turn, is affected by pill burden, patient satisfaction and patient preference.

Currently, under the Centers for Medicare and Medicaid Services (CMS) ESRD Prospective Payment System (PPS),dialysis centers are reimbursed separately for oral medications. However, CMS has proposed that from 2016 these drugs will be included in the PPS composite rate payment for dialysis services. It will therefore be particularly useful to analyze these data with regard to Medicare cost impact. Also, because of the importance of quality of life for dialysis patients, the 2008 Medicare Conditions for Coverage mandate health-related quality of life (HR-QOL) be measured annually and addressed [26]. High pill burden has been shown to be negatively associated with HR-QOL [22] and reducing pill burden may be a mechanism to improve HR-QOL, as well as laboratory measures, in dialysis patients.

This study is not without limitations. First, this cross-sectional study highlights statistically significant associations, but cannot determine causality. Lower pill burden and higher efficiency in patients with higher MPRs may arise from higher adherence to both prescribed PBs and recommended dietary restrictions. Second, the MPR is the most commonly used and best-known measure of adherence but is only a proxy for adherence. Third, the MPR has a limited ability to analyze the continuity of medication usage. The MPR assumes that patients reorder only if they have no more pills but in fact they can throw away or store pills and reorder on the appropriate date to appear compliant to their physician. Therefore, a high MPR does not necessarily guarantee high adherence. However, a low MPR is a good indication that patients are not compliant as they do not have enough medications to stay adherent to their prescriptions. Patients in the high pill burden group may be more likely to continue to get refills even if they have not taken all their pills. Chiu *et al.* also found ∼60% adherence in patients with a PB pill burden of 13–32 pills/day. Finally, the study is limited by the fact that pill burden is confounded with PB type. We did not investigate binder type or dual binder therapy in the current analysis due to the complexity of calculating the MPR from numerous different start and stop dates for different binders for a single patient.

In summary, using data from the pharmacy management program, we found that overall MPR is low and the MPR increases as pill burden decreases. The pattern of results supports the hypothesis that lower pill burden is associated with higher adherence, as assessed by the MPR. A higher MPR was associated with lower mean phosphorus levels and higher percentage of patients with phosphorus ≤5.5 mg/dL. The conclusion that PB formulations which provide equivalent phosphate binding capacity with lower pill burden is likely to achieve superior adherence and better phosphorus control is plausible and in agreement with existing studies that fewer pills or doses resulted in better compliance [27, 28]. Allowing patients to control or improve their own compliance with lower pill burden may be accomplished through changes in PB type or potentially through new types of PBs.

ACKNOWLEDGEMENTS

We thank DaVita Clinical Research (DCR) for providing the clinical data, analysis and writing support for this research project and specifically Karen Spach, PhD, and Abigail Hunt, PhD, for editorial contributions to this manuscript. DCR is committed to advancing the knowledge and practice of kidney care. These data were originally presented in poster form at the 49th European Renal Association-European Dialysis and Transplant Association Congress, in Paris, France on 25 May 2012 and at the National Kidney Foundation Spring Clinical Meeting in Orlando, FL, USA on 3 April 2013.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

S.W. and T.A. were employees of DaVita Clinical Research (DCR) at the time of the study. K.R. is a current employee of DCR. P.B. is an employee of Vifor Fresenius Medical Care Renal Pharma. B.N. is a physician at Denver Nephrology (Denver, CO). This study was sponsored by Vifor Fresenius Medical Care Renal Pharma.

REFERENCES

1. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003; 42: S1–S201
2. Karamanidou C, Clatworthy J, Weinman J *et al.* A systematic review of the prevalence and determinants of nonadherence to phosphate binding medication in patients with end-stage renal disease. BMC Nephrol 2008; 9: 2
3. Block GA, Hulbert-Shearon TE, Levin NW *et al.* Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31: 607–617
4. Marchais SJ, Metivier F, Guerin AP *et al.* Association of hyperphosphataemia with haemodynamic disturbances in end-stage renal disease. Nephrol Dial Transplant 1999; 14: 2178–2183
5. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 1990; 15: 458–482
6. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int 2006; 70: 771–780
7. Saran R, Bragg-Gresham JL, Rayner HC *et al.* Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. Kidney Int 2003; 64: 254–262
8. Tentori F, Blayney MJ, Albert JM *et al.* Mortality risk for dialysis patients with different levels of serum calcium, phosphorus and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2008; 52: 519–530
9. Menon V, Greene T, Pereira AA *et al.* Relationship of phosphorus and calcium–phosphorus product with mortality in CKD. Am J Kidney Dis 2005; 46: 455–463

10. Isakova T, Gutierrez OM, Chang Y *et al*. Phosphorus binders and survival on hemodialysis. J Am Soc Nephrol 2009; 20: 388–396
11. Benner D, Nissenson AR, Van Wyck D. Focused clinical campaign improves mineral and bone disorder outcomes. J Ren Care 2012; 38: 2–8
12. Port FK, Pisoni RL, Bommer J *et al*. Improving outcomes for dialysis patients in the International Dialysis Outcomes and Practice Patterns Study. Clin J Am Soc Nephrol 2006; 1: 246–255
13. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney Int Suppl 2009; 113: S1–S130
14. Toussaint ND, Pedagogos E, Beavis J *et al*. Improving CKD-MBD management in haemodialysis patients: barrier analysis for implementing better practice. Nephrol Dial Transplant 2011; 26: 1319–1326
15. Weed-Collins M, Hogan R. Knowledge and health beliefs regarding phosphate-binding medication in predicting compliance. ANNA J 1989; 16: 278–282, 285, discussion 286
16. Milas NC, Nowalk MP, Akpele L *et al*. Factors associated with adherence to the dietary protein intervention in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 1995; 95: 1295–1300
17. Cianciaruso B, Capuano A, D'Amaro E *et al*. Dietary compliance to a low protein and phosphate diet in patients with chronic renal failure. Kidney Int Suppl 1989; 27: S173–S176
18. Bame SI, Petersen N, Wray NP. Variation in hemodialysis patient compliance according to demographic characteristics. Soc Sci Med 1993; 37: 1035–1043
19. Morduchowicz G, Sulkes J, Aizic S *et al*. Compliance in hemodialysis patients: a multivariate regression analysis. Nephron 1993; 64: 365–368
20. Arenas MD, Malek T, Alvarez-Ude F *et al*. Phosphorus binders: preferences of patients on haemodialysis and its impact on treatment compliance and phosphorus control. Nefrologia 2010; 30: 522–530
21. Arenas MD, Malek T, Gil MT *et al*. Challenge of phosphorus control in hemodialysis patients: a problem of adherence?. J Nephrol 2010; 23: 525–534
22. Chiu YW, Teitelbaum I, Misra M *et al*. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. Clin J Am Soc Nephrol 2009; 4: 1089–1096
23. Peterson AM, Nau DP, Cramer JA *et al*. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007; 10: 3–12
24. Leslie R. Calculating Medication Compliance, Adherence and Persistence in Administrative Pharmacy Claims Databases. In Proceedings of the Western Users of SAS Software Meeting. 5–7 November 2008, Universal City, CA, USA.
25. Mehrotra R, Martin KJ, Fishbane S *et al*. Higher strength lanthanum carbonate provides serum phosphorus control with a low tablet burden and is preferred by patients and physicians: a multicenter study. Clin J Am Soc Nephrol 2008; 3: 1437–1445
26. Department of Health and Human Services, Centers for Medicare and Medicaid Services. Medicare and Medicaid programs; Conditions for coverage for ESRD facilities, Final Rule. Fed Regist 2008; 73: 20370–20484
27. Lindberg M, Lindberg P. Overcoming obstacles for adherence to phosphate binding medication in dialysis patients: a qualitative study. Pharm World Sci 2008; 30: 571–576
28. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23: 1296–1310

Received for publication: 20.12.2012; Accepted in revised form: 11.5.2013

ORIGINAL ARTICLE

Nephrol Dial Transplant (2014) 29: 2099–2105
doi: 10.1093/ndt/gfu101
Advance Access publication 29 April 2014

Association of fibroblast growth factor-23 with arterial stiffness in the Multi-Ethnic Study of Atherosclerosis

Jeffrey J. Hsu[1], Ronit Katz[3], Joachim H. Ix[2], Ian H. de Boer[4], Bryan Kestenbaum[4] and Michael G. Shlipak[1]

[1]Division of General Internal Medicine, San Francisco VA Medical Center, University of California, San Francisco, CA, USA, [2]Division of Nephrology, Department of Medicine, University of California, San Diego, La Jolla, CA, USA, [3]Department of Biostatistics, University of Washington, Seattle, WA, USA and [4]Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA, USA

Correspondence and offprint requests to: Michael G. Shlipak; E-mail: michael.shlipak@ucsf.edu

ABSTRACT

Background. Serum fibroblast growth factor-23 (FGF-23) is associated with cardiovascular disease (CVD), yet the mechanisms remain uncertain. Our objective was to determine whether higher FGF-23 concentrations are associated with arterial stiffness.

Methods. In this cross-sectional study, serum FGF-23 concentrations were measured in 5977 participants without known CVD in the Multi-Ethnic Study of Atherosclerosis. The primary outcomes of interest were large (LAE) and small artery elasticity (SAE), pulse pressure and ankle-brachial index (ABI) > 1.30. LAE and SAE were measured by pulse contour analysis of the radial artery. Pulse pressure was measured with an automated sphygmomanometer using the average of two