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Prescription characteristics of phosphate binders in a high pill burden for hemodialysis patients

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Abstract

Background: Dialysis patients have to take many oral drugs, causing a high pill burden. Phosphate binders (PBs) account for a large proportion of daily pill burden; however, the relationship between patient background and prescription status of PBs is not clear.

Methods: We clarified the characteristics of PBs in the total daily pill burden by analyzing the drugs prescribed for 533 chronic hemodialysis patients in our facility.

Results: An average of nine different types of oral drugs was prescribed for each patient. The mean and median values of total pill burden were 15.1 and 14.1 pills/day/patient, respectively. The total pill burden showed a significant negative correlation with age and a significant positive correlation with dialysis vintage. In addition, the total pill burden was significantly higher in males than in females. However, there was no difference in the pill burden between patients with and without diabetes mellitus (DM). PBs were prescribed to 409 patients (76.7%), and the mean pill burden derived from PBs was 6.44 pills/day/patient. This was by far the highest of all 35 different drug categories and accounted for 32.84% of all pills. Multiple regression analysis demonstrated that independent predictors of total pill burden were age, dialysis vintage, DM, and serum phosphorus (P) levels, and all these variables, except DM, were also independent predictors of pill burden from PBs. These variables were also selected when considering the use of calcimimetics.

Conclusions: A high pill burden is more likely to occur in younger patients with longer dialysis vintage, DM, higher serum P levels, and prescription of calcimimetics. In addition, PB was the single largest contributor to the total pill burden that positively and linearly linked to serum P levels. Therefore, P management is a high-priority issue in the mitigation of high pill burdens in dialysis patients.

Keywords: High pill burden, Polypharmacy, Phosphate binder, Calcimimetics, Hemodialysis patients, Serum phosphorus levels

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Background

Polypharmacy causes a variety of problems, including adverse drug interaction events, lower quality of life, inappropriate (incorrect, over-, and under-) prescriptions, poor medication adherence, and increased health care costs [1–3]. Although there is currently no clear-cut definition of polypharmacy [2, 4], chronic dialysis patients have to take many pills of oral drugs, as such bear high pill burden, to treat multiple comorbidities [5–12]. The symptoms and severity of complications vary greatly among dialysis patients. Therefore, it is considered that a situation of high pill burden would be affected by the patient background such as gender, age, dialysis vintage, and presence or absence of diabetes mellitus (DM).

It has been reported that phosphate binders (PBs) account for a large proportion of the daily pill burden in dialysis patients [6, 10, 11]. However, there are few studies clarifying the relationship between patient background and prescription status of PBs in a high pill burden. In addition, some new PBs and calcimimetics have recently become available for the treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) in dialysis patients. In this study, we investigated the characteristics of PBs in cases of high pill burden by analyzing the drugs prescribed for 533 chronic hemodialysis patients in Japan.

Methods

Study design

This single-center cross-sectional study was approved by the Hidaka Hospital Medical Ethics Committee. Out of 546 chronic hemodialysis patients at our dialysis center of the Heisei Hidaka clinic (Gunma, Japan), we excluded 13 patients who were not on stable hemodialysis (3 times a week) due to surgery or hospitalization during the study period (February 2020). Because we had observed small increases in serum phosphorus (P) levels in our dialysis patients at the end and beginning of every year, we avoided this period and set the study period in February. We analyzed the drug prescription records and routine blood chemistries (serum corrected calcium [Ca], P, and intact parathyroid hormone [i-PTH] levels) of 533 patients who were prescribed at least one pill for 1 month.

Classification of oral drugs

The oral drugs were basically classified according to the drug efficacy classification numbers of Standard Commodity Classification for Japan (JSCC; under the jurisdiction of Ministry of Internal Affairs and Communications) [13] described in each drug package insert. As exceptions, PBs and potassium binders are both denoted by 87219 as "other cardiovascular agents" and calcimimetics (evocalcet [14, 15]) is denoted by 873999 as "other agents affecting metabolism, not elsewhere classified," so they were independently classified as "PBs," "potassium binders," and "calcimimetics." Vitamin preparations were divided into two categories of "vitamin D receptor activator (VDRA)" and "vitamin preparations (exc. VDRA)." Antibiotic preparations and synthetic antimicrobials were represented as "antimicrobials." A compounded drug consisting of two different categories was classified into the main therapeutic category. The 18 categories of drugs prescribed to less than 10 patients for 1 month were collectively classified as "others." As a result, 269 different types of oral drugs (322 types, including different dose formulations) were classified into 35 categories.

Total pill burden

The dosage units of tablets, capsules, packets (for powder, granule, and dry syrup), small plastic cups (for jelly), and small plastic vials (for oral solution) prescribed for 1 month were all counted as one pill for convenience of calculation. Troches, gargles, nutritional drinks, inhalants, and oral ointments were excluded from the count.

The total number of pills of all drugs prescribed for 533 patients for 1 month was calculated (all pills). Similarly, the number of pills prescribed for 1 month was totaled in each drug category (categorized pills). The ratio (%) of categorized pills to all pills was calculated and then ranked from 1st to 35th. Also, the number of patients was counted for each drug category. "Total pill burden" was defined as how many all pills were prescribed per patient per day. Similarly, the daily pill burden derived from drugs belonging to category A was defined as "pill burden from A."

PBs

Ca carbonate, lanthanum (La) carbonate, ferric citrate hydrate, sucroferric oxyhydroxide, sevelamer hydrochloride (HCl), and bixalomer were prescribed during the study period in our facility. Because the number of prescribed patients was relatively small, total pills of ferric citrate hydrate (74 patients) and sucroferric oxyhydroxide (31 patients) were expressed as the pill burden from "iron (Fe)-based PBs." Similarly, total pills of sevelamer HCl (20 patients) and bixalomer (19 patients) were expressed as the pill burden from "polymeric PBs." For further analysis, PBs were classified into two categories: Ca-based PBs (Ca carbonate) and non-Ca-based PBs (PBs other than Ca carbonate).

CKD-MBD-related drugs

We examined whether the prescription of CKD-MBD-related drugs excluding PBs would affect the total pill burden and pill burden from PBs. The following oral and intravenous (IV) calcimimetics and VDRAs used at our facility were defined as CKD-MBD-related drugs: oral calcimimetics: evocalcet [14, 15]; oral VDRA:

alfacalcidol and calcitriol; IV calcimimetics: etelcalcetide HCl [15]; and IV VDRA: calcitriol and maxacalcitol (22-oxacalcitriol) [16].

Statistical analyses

For numerical variables, normality was checked using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were expressed as median (interquartile range). Although the number of pills was non-normally distributed data, it was expressed as the mean values instead of the median values in order to make the difference clear.

A two-group comparison was performed with the Fisher exact test, unpaired *t* test, or the Mann–Whitney *U* test. A single correlation was analyzed using Spearman's correlation analysis. Additionally, the age and dialysis vintage were divided into quintiles, and the Kruskal–Wallis test was used for comparisons between quintiles. Multiple regression analysis was performed using a stepwise method. Statistical analysis was performed using SPSS software (version 21, IBM, NY, USA). *P* values less than 0.05 were considered statistically significant.

Results

Total pill burden

The patient background, dialysis condition, serum chemistries, comorbidities, and total prescription status of the 533 patients are shown in Table 1. Approximately 9 different types of oral drugs out of 269 types were prescribed per patient for a month. The mean and median values of total pill burden were 15.1 ± 7.6 and 14.1 (10.0–18.7) pills/day/patient, respectively.

The total pill burden negatively correlated with age and positively correlated with dialysis vintage, serum P levels, serum albumin (Alb) levels, and normalized protein catabolic rate (nPCR) (Table 2). Similarly, the quintile analysis clearly showed that the total pill burden gradually decreased with age and increased with dialysis vintage (Fig. 1). The total pill burden was significantly higher in males than in females; however, there was no difference in the pill burden between patients with and without DM (Fig. 2 and Table 3).

Pill burden from each drug category

PBs were prescribed to the largest number of patients, 409 patients (76.7%), and the mean value of the pill burden from PBs was 6.44 pills/day/patient (Table 4). This was by far the highest and accounted for 32.84% of all pills. In individual PBs, Ca carbonate constituted about half of all PBs and also accounted for 16.37% of all pills. The second-largest contributor was "antihypertensives," which accounted for only 8.36% of all pills. In oral CKD-MBD-related drugs, "calcimimetics" ranked 11th and "VDRA" ranked 14th. The pill burden from both PBs and oral CKD-MBD-related drugs accounted for 36.86% of all pills.

Pill burden from all PBs

The pill burden from all PBs showed a negative correlation with age and positive correlations with dialysis vintage, serum P levels, serum Alb levels, and nPCR (Table 2). These results were similar to those observed in the total pill burden. The quintile analysis also clearly showed that the pill burden from PBs, the single largest contributor, gradually decreased with age and increased with dialysis vintage (Fig. 1). There was no significant difference in the percentage of patients treated with PBs between males and females and between patients with and without DM (Table 3). In contrast, the pill burden from PBs was significantly higher in males and in non-DM patients than in females and DM patients, respectively (Fig. 2 and Table 3).

Pill burden from individual PBs

The pill burden from Ca carbonate negatively correlated with age and positively correlated with dialysis vintage and serum P levels (Table 2). Similarly, the pill burden from La carbonate correlated with age and serum P levels, and Fe-based PBs correlated with age and dialysis vintage. Fewer patients were prescribed polymeric PBs (Tables 3 and 4), and the pill burden from polymeric PBs was not correlated with any variable (Table 2).

The percentage of patients who were prescribed Ca carbonate did not differ between males and females and between patients with and without DM, while more pills were prescribed in non-DM patients than in DM patients (Table 3). La carbonate was more prescribed in males and in non-DM patients than in females and DM patients, respectively.

CKD-MBD-related drugs

The total pill burden was significantly higher in both oral and IV calcimimetics users when compared with non-users (Table 5). Similar results were observed in the pill burden from all PBs. On the other hand, only in oral calcimimetics users, the pill burden from both Ca-based and non-Ca-based PBs was significantly higher. The pill burden from all PBs and from Ca-based PB in oral VDRAs users was less than those in non-users.

Multiple regression analysis

Multiple regression analysis showed that independent predictors of total pill burden were age, dialysis vintage, DM, and serum P levels, and all these variables, except DM, were also independent predictors of pill burden from PBs (Table 6). This result was also consistent when

Table 1 Patient background, dialysis condition, serum chemistries, comorbidities, and prescription status

Patients	n	533
Gender (male)	n (%)	362 (67.9)
Age	years	71.3 (63.8-78.0)
Dialysis vintage	years	5.5 (2.1-10.8)
Age of starting dialysis	years	63.9 (52.8-73.1)
Dialysis Modality		
HD	n (%)	306 (57.4)
On-line HDF	n (%)	227 (42.6)
Time		
< 4 hr	n (%)	74 (13.9)
4 hr	n (%)	443 (83.1)
4.5 hr ≤	n (%)	16 (3.0)
Blood flow		
< 200 mL/min	n (%)	105 (19.7)
200 mL/min	n (%)	214 (40.2)
210 mL/min ≤	n (%)	214 (40.2)
Dialysate Ca		
2.5 mEq/L	n (%)	365 (68.5)
3.0 mEq/L	n (%)	168 (31.5)
Serum corrected Ca	mg/dL	8.70 ± 0.61
Serum P	mg/dL	5.37 ± 1.17
Serum i-PTH	pg/mL	182 (120-257)
Comorbidities		
Diabetes mellitus (DM)	n (%)	310 (58.2)
Heart failure	n (%)	155 (29.1)
Angina	n (%)	85 (15.9)
Myocardial infarction	n (%)	26 (4.9)
Arrhythmia / Extrasystes	n (%)	80 (15.0)
Peripheral vascular disease	n (%)	88 (16.5)
Cerebral / Brainstem infarction	n (%)	106 (19.9)
Neurologic / Psychiatric disease	n (%)	78 (14.6)
Insomnia	n (%)	92 (17.3)
Gastointestinal disease	n (%)	332 (62.3)
Constipation	n (%)	141 (26.5)
Diarrhea	n (%)	24 (4.5)
Respiratory disease	n (%)	92 (17.3)
Hepatobiliary disease	n (%)	132 (24.8)
Pancreatic disease	n (%)	27 (5.1)
Thyroid disease	n (%)	52 (9.8)
Ocular disease	n (%)	263 (49.3)
Joint and bone disease	n (%)	221 (41.5)
Previous fracture	n (%)	65 (12.2)
Malignancy (including history)	n (%)	135 (25.3)
Gangrene, Cellulitis, Decubitus, Skin ulcer	n (%)	31 (5.8)
Previous parathyroidectomy (PTx)	n (%)	10 (1.9)
Prescription medical doctors	n	26
Different types of oral drugs		
mean±SD	types/month/patient	9.2 ± 3.2
median (Q1-Q3)	types/month/patient	9 (7-11)
Total pill burden		
mean±SD	pills/day/patient	15.1 ± 7.6
median (Q1-Q3)	pills/day/patient	14.1 (10.0-18.7)

HD hemodialysis, *HDF* hemodialysis filtration, *Q1* first quartile, *Q3* third quartile

adding the use of calcimimetics to the independent variables in model 2. The prescriptions of oral and IV calcimimetics were independent positive predictors of the total pill burden. In addition, the use of oral calcimimetics was also an independent positive predictor of the pill burden from PBs.

Discussion

The present study highlights some important results that could lead to a clue to reduce the high pill burden in dialysis patients as follows: The independent predictors of total pill burden were age, dialysis vintage, DM, and serum P levels, and all these variables except DM were also independent predictors of the pill burden from PBs. In addition, these variables were also selected when considering the use of calcimimetics. Furthermore, PB was the single largest contributor to the total pill burden that positively and linearly linked to serum P levels. Therefore, P management is a high-priority issue in the mitigation of high pill burdens in dialysis patients.

Nine different types of oral drugs were prescribed to our patients. This is less than those found in other previous reports [5, 11] and is similar to one report [6]. In addition to the differences in approved drugs between countries, prescribed drug types depend on the severity of patients between large general hospitals and outpatient maintenance hemodialysis facilities. Furthermore, many new drugs have recently been launched in the market. Therefore, it is obvious that the number of drug types prescribed for dialysis patients varies depending on countries, facility types, and years in which they were reported. On the other hand, the present result (9 types) is slightly higher than that in European CKD patients not on dialysis (8 types) [17, 18]. Thus, it is intriguing to examine consecutive changes in the number of drug

Table 2 Single correlation analyses among patient background, total pill burden, and pill burden from PBs

	Age		Dialysis vintage		Serum corrected Ca		Serum P		Serum i-PTH		Serum Alb		nPCR	
	(r)	(*P*)	(r)	(*P*)	(r)	(*P*)	(r)	(*P*)	(r)	(*P*)	(r)	(*P*)	(r)	(*P*)
Age (years)	—	—	- 0.128	0.003	0.054	0.216	-0.249	< 0.001	-0.148	0.003	-0.333	< 0.001	-0.056	0.207
Dialysis vintage (years)	- 0.128	0.003	—	—	0.128	0.004	0.023	0.600	-0.025	0.610	-0.014	0.752	0.110	0.012
Serum parameters														
Corrected Ca (mg/dL)	0.054	0.216	0.128	0.004	—	—	-0.056	0.200	-0.308	< 0.001	-0.098	0.026	-0.013	0.763
P (mg/dL)	- 0.249	< 0.001	0.023	0.600	-0.056	0.200	—	—	0.194	< 0.001	0.179	<0.001	0.277	<0.001
i-PTH (pg/mL)	- 0.148	0.003	- 0.025	0.610	-0.308	< 0.001	0.194	< 0.001	—	—	0.024	0.623	0.051	0.307
Total pill burden (pills/day/patient)	- 0.192	< 0.001	0.314	< 0.001	-0.038	0.391	0.198	< 0.001	0.004	0.942	0.118	0.007	0.090	0.040
Pill burden from all PBs (pills/day/patient)	- 0.344	< 0.001	0.238	< 0.001	-0.031	0.530	0.188	< 0.001	0.084	0.126	0.152	0.002	0.119	0.018
Pill burden from individual PBs														
Ca carbonate (pills/day/patient)	-0.287	<0.001	0.251	<0.001	-0.099	0.090	0.238	<0.001	0.037	0.567	0.114	0.050	0.068	0.248
La carbonate (pills/day/patient)	-0.252	0.001	0.123	0.115	-0.100	0.202	0.181	0.021	0.030	0.729	0.088	0.266	0.079	0.322
Fe-based PBs (pills/day/patient)	-0.277	0.004	0.236	0.016	-0.054	0.589	-0.058	0.561	0.047	0.661	0.187	0.058	-0.056	0.575
Polymeric PBs (pills/day/patient)	- 0.238	0.145	0.201	0.219	-0.208	0.211	0.151	0.367	0.013	0.944	-0.100	0.549	0.119	0.482

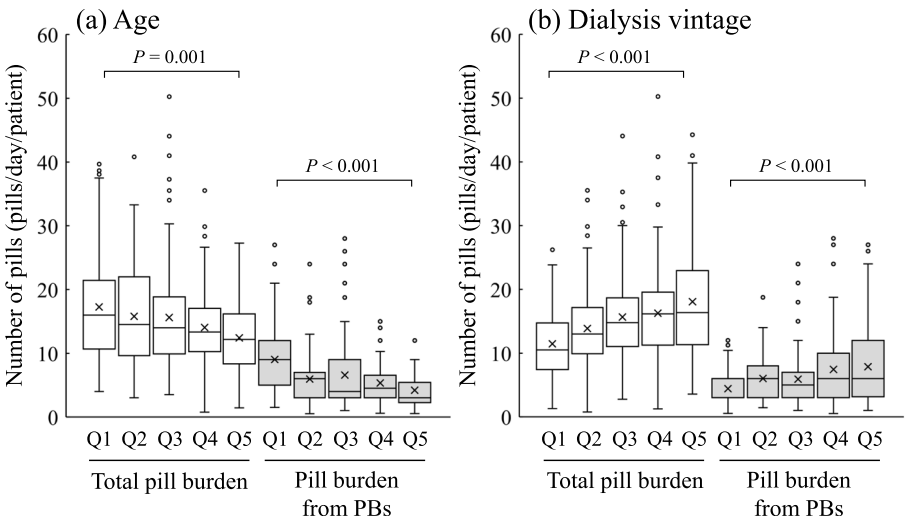

Fig. 1 Total pill burden (white columns) and pill burden from PBs (gray columns) in quintiles by age (**a**) and dialysis vintage (**b**). Q1–5; first–fifth quintiles

types prescribed before and after the initiation of dialysis in the same cohorts.

The mean (15.1) and median (14.1) values of the total pill burden in this study are lower than those in previous reports [6, 8, 10–12]. On the other hand, the pill burden from PBs (mean 6.4 pills) is much less than those found in other two reports [6, 11] and only slightly fewer than that (mean 6.7 pills) in Japan in the international Dialysis Outcomes and Practice Patterns Study (DOPPS) [9]. Therefore, it is confirmed that the PB prescription status at our facility is almost average in Japan. However, a simple comparison with the past investigation may not make much sense, because new types of PBs such as ferric citrate hydrate, sucroferric oxyhydroxide, and bixalomer are now available. The proportion of PBs in all pills (32.84%) was much lower than those in other facilities [6, 11], although it is a consistent result that this is an outstandingly high proportion compared to other drug categories [6, 10, 11]. In our facility, IV calcimimetics (etelcalcetide HCl) and new oral calcimimetics (evocalcet) [14, 15] have been actively used, and thus, serum i-PTH levels in 63.1% of patients were within the target range of the Japanese Society for Dialysis Therapy (JSDT) guidelines (60–240 pg/mL) [19]. Lower PTH reduces P mobilization from the bone and facilitates P management. In addition, we enthusiastically provide

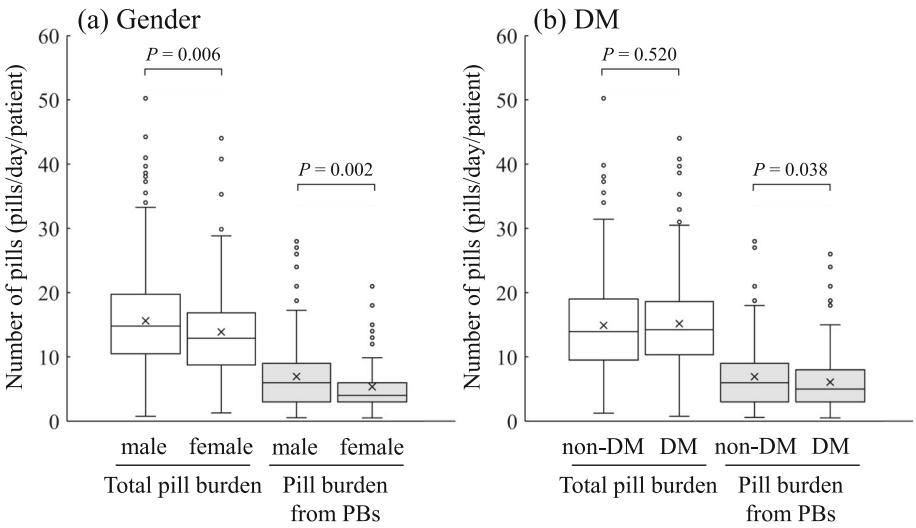

Fig. 2 Comparison of total pill burden (white columns) and pill burden from PBs (gray columns) between males and females (**a**) and presence and absence of DM (**b**)

Table 3 Comparison of patient background, total pill burden, number of patients, and pill burden from PBs between males and females and presence and absence of DM

		Total	Gender (male)	Gender (female)		non-DM	DM	
		533(100%)	362 (67.9%)	171 (32.1%)	(*P*)	223 (41.8%)	310 (58.2%)	(*P*)
Age	years	71.3 (63.8-78.0)	70.4 (61.2-76.0)	73.3 (66.7-81.5)	< 0.001	72.3 (64.4-79.4)	71.0 (63.0-76.2)	0.093
Diabetes (yes)	n (%)	310 (58.2)	224 (61.9)	86 (50.3)	0.008	—	—	—
Dialysis vintage	years	5.5 (2.1-10.8)	6.1 (2.1-11.4)	4.5 (2.2-9.1)	0.094	8.2 (2.9-17.1)	4.5 (1.8-7.7)	< 0.001
Serum MBD parameters								
Corrected Ca	mg/dL	8.70 ± 0.61	8.61 ± 0.62	8.88 ± 0.55	< 0.001	8.74 ± 0.63	8.67 ± 0.60	0.258
P	mg/dL	5.37 ± 1.17	5.42 ± 1.22	5.27 ± 1.04	0.174	5.51 ± 1.19	5.27 ± 1.14	0.019
i-PTH	pg/mL	182 (120-257)	189 (132-260)	168 (107-252)	0.091	182 (122-267)	183 (117-256)	0.596
Nutritional status								
Serum Alb	g/dL	3.78 ± 0.33	3.81 ± 0.33	3.72 ± 0.33	0.002	3.79 ± 0.33	3.78 ± 0.34	0.913
nPCR	g/kg/day	0.772 ± 0.139	0.758 ± 0.132	0.800 ± 0.150	0.001	0.795 ± 0.137	0.755 ±0.139	0.003
Total pill burden (mean)	pills/day/patient	15.1± 7.6	15.6 ± 7.8	13.9 ± 7.1	0.006	14.9 ± 7.7	15.2 ± 7.5	0.520
Total pill burden (median)	pills/day/patient	14.1 (10.0-18.7)	14.8 (10.5-19.7)	12.9 (8.8-16.8)	0.006	13.9 (9.6-18.9)	14.2 (10.4-18.6)	0.520
Number of patients								
All PBs	n (%)	409 (76.7)	279 (77.1)	130 (76.0)	0.435	178 (79.8)	231 (74.5)	0.092
Individual PBs								
Ca carbonate	n (%)	301 (56.5)	207 (57.2)	94 (55.0)	0.349	133 (59.6)	168 (54.2)	0.122
La carbonate	n (%)	164 (30.8)	124 (34.3)	40 (23.4)	0.007	81 (36.3)	83 (26.8)	0.012
Fe-based PBs	n (%)	104 (19.5)	75 (20.7)	29 (17.0)	0.183	38 (17.0)	66 (21.3)	0.133
Polymeric PBs	n (%)	39 (7.3)	28 (7.7)	11 (6.4)	0.365	16 (7.2)	23 (7.4)	0.528
Pill burden from PBs								
All PBs	pills/day/patient	6.44 ±4.78	6.94 ± 5.08	5.36 ± 3.87	0.002	6.92 ± 4.94	6.08 ± 4.64	0.038
Individual PBs								
Ca carbonate	pills/day/patient	4.36 ± 2.01	4.47 ± 2.11	4.12 ± 1.77	0.298	4.64 ± 2.04	4.15 ± 1.97	0.035
La carbonate	pills/day/patient	3.98 ± 2.14	4.09 ± 2.17	3.64 ± 2.03	0.190	4.25 ± 2.28	3.72 ± 1.97	0.103
Fe-based PBs	pills/day/patient	4.14 ± 2.40	4.40 ± 2.53	3.47 ± 1.93	0.066	4.22 ± 3.17	4.09 ± 1.85	0.511
Polymeric PBs	pills/day/patient	6.10 ± 3.34	6.23 ± 3.45	5.77 ± 3.20	0.633	6.88 ± 3.23	5.56 ± 3.38	0.301

dietary education to dialysis patients. Therefore, this may be the reason why the pill burden from PBs was lesser and the proportion of patients prescribed PBs (76.7%) was also lower when compared to the results of another DOPPS (88% of patients are prescribed PBs in 12 countries) [20].

The total pill burden linearly correlated with decreased age and with increased dialysis vintage and was more prevalent in males. These relationships were also observed in the pill burden from PBs. On the other hand, there was no difference in the total pill burden between DM and non-DM patients, although the pill burden from PBs was significantly more prevalent in non-DM patients. The pill burden from "antidiabetic agents" was 2.27 pills and ranked sixth in the list of contributors accounting for 4.95% of all pills. The "antidiabetic agents" were prescribed to only DM patients. In addition, serum P levels in DM patients were significantly lower than those in non-DM patients. This result is probably due to reduced dietary intake volume, because nPCR was significantly lower in DM patients than in non-DM patients. Thus, DM patients were prescribed lower pills from PBs instead of higher pills from "antidiabetic agents." Therefore, it is considered that there is no significant difference in the total pill burden between patients with and without DM. The above consideration is consistent with the multiple regression analysis showing that independent predictors of total pill burden were age, dialysis vintage, DM, and serum P levels, and these variables, except DM, were also independent predictors of the pill burden from PBs. These can also be explained by the fact that PB is the single largest contributor to the total pill burden.

The uses of oral and IV calcimimetics increased both the total pill burden and the pill burden from all PBs. This result can be explained as follows. First, the pill

Table 4 Pill burden from each drug category

Categories of oral drugs (35 different types)		Pill burden and number of prescribed patients			
		Total pills (%)	Patients (n)	Patients (%)	Daily pills (pills/day/patient)
1	Phosphate binders	32.84	409	76.7	6.44
	Ca carbonate	16.37	301	56.5	4.36
	La carbonate	8.14	164	30.8	3.98
	Fe-based PBs	5.37	104	19.5	4.14
	Polymeric PBs	2.97	39	7.3	6.10
2	Antihypertensives	8.36	329	61.7	2.04
3	Coronary vasodilators, antianginal agents	8.12	308	57.8	2.12
4	Anticoagulants	6.06	269	50.5	1.81
5	Agents for peptic ulcer	5.52	307	57.6	1.44
6	Antidiabetic agents	4.95	175	32.8	2.27
7	Purgatives and clysters	3.47	153	28.7	1.82
8	Antidiarrheals, intestinal regulators	2.82	94	17.6	2.40
9	Agents for hyperlipidemias	2.48	189	35.5	1.05
10	Potassium binders	2.33	98	18.4	1.90
11	Calcimimetics	2.30	155	29.1	1.18
12	Antiarrhythmic agents	2.00	93	17.4	1.72
13	Hypnotics and sedatives, antianxietics	1.98	138	25.9	1.15
14	Vitamin D receptor activator (VDRA)	1.72	141	26.5	0.98
15	Diuretics	1.67	118	22.1	1.13
16	Antipyretics, analgesics and anti-inflammatory agents	1.46	83	15.6	1.41
17	Antiallergic agents	1.16	94	17.6	0.99
18	Vitamin preparations (exc. VDRA)	1.16	36	6.8	2.59
19	Chinese medicines	1.04	76	14.3	1.10
20	Cholagogues	0.78	18	3.4	3.47
21	Antihypotensive agents	0.71	91	17.1	0.63
22	Antitussives and expectorants	0.58	35	6.6	1.32
23	Anti-itchings	0.56	34	6.4	1.33
24	Antidysuria agents	0.56	30	5.6	1.51
25	Gastrointestinal prokinetic agents	0.56	25	4.7	1.79
26	Psychotropic agents	0.54	28	5.3	1.54
27	Agents for treatment of gout	0.50	43	8.1	0.93
28	Antiepileptics	0.42	20	3.8	1.70
29	Thyroid preparations	0.41	26	4.9	1.28
30	Adrenal hormone preparations	0.35	17	3.2	1.65
31	Pain relieving agents	0.32	24	4.5	1.06
32	Zinc preparations	0.27	18	3.4	1.19
33	Antimicrobials	0.12	19	3.6	0.52
34	Agents used for common cold	0.12	18	3.4	0.53
35	Others (less than 10 prescribed-patients)	1.77	63	11.8	2.25

Table 5 Comparison of total pill burden and pill burden from PBs between users and non-users of oral/IV calcimimetics and VDRAs. PBs were further analyzed separately for Ca-based PB (Ca carbonate) and non-Ca-based PBs (PBs other than Ca carbonate)

	Prescription	Patients	Total pill burden		Pill burden from all PBs		Pill burden from Ca-based PB		Pill burden from non-Ca-based PBs	
	yes/no	n (%)	pills/day/patient	(*P*)	pills/day/patient	(*P*)	pills/day/patient	(*P*)	pills/day/patient	(*P*)
Oral calcimimetics	Non-user	378 (70.9)	13.9 ± 6.7	< 0.001	5.77 ± 4.13	< 0.001	4.03 ± 1.91	< 0.001	4.49 ± 2.87	0.020
(evocalcet)	User	155 (29.1)	17.8 ± 8.7		7.80 ± 5.66		5.05 ± 2.06		5.75 ± 4.29	
IV caclimimetics	Non-user	462 (86.7)	14.8 ± 7.6	0.005	6.26 ± 4.74	0.040	4.29 ± 2.03	0.074	4.87 ± 3.54	0.209
(etelcalcetide HCl)	User	71 (13.3)	16.9 ± 7.0		7.43 ± 4.92		4.79 ± 1.84		5.31 ± 3.31	
Oral VDRAs	Non-user	392 (73.5)	15.4 ± 8.0	0.208	6.81 ± 4.96	0.001	4.57 ± 1.98	< 0.001	5.00 ± 3.69	0.701
(calcitriol, alfacalcidol)	User	141 (26.5)	14.1 ± 6.3		5.36 ± 4.08		3.68 ± 1.98		4.78 ± 2.82	
IV VDRAs	Non-user	245 (46.0)	14.6 ± 7.2	0.360	6.12 ± 4.70	0.088	4.16 ± 2.11	0.054	5.06 ± 3.31	0.476
(calcitriol, maxacalcitol)	User	288 (54.0)	15.4 ± 7.9		6.68 ± 4.84		4.52 ± 1.93		4.88 ± 3.62	

Table 6 Multiple regression analyses accounting for factors that affect total pill burden and pill burden from PBs

		Model 1		Model 2	
		Total pill burden (pills/day/patient)	Pill burden from PBs (pills/day/patient)	Total pill burden (pills/day/patient)	Pill burden from PBs (pills/day/patient)
Gender (male)	β		0.097		
	(*P*)		0.040		
Age (years)	β	- 0.110	- 0.250	- 0.090	- 0.255
	(*P*)	0.011	< 0.001	0.037	< 0.001
Dialysis vintage (years)	β	0.290	0.175	0.220	0.145
	(*P*)	< 0.001	< 0.001	< 0.001	0.003
DM (yes)	β	0.135		0.141	
	(*P*)	0.003		0.001	
Serum P (mg/dL)	β	0.210	0.144	0.196	0.140
	(*P*)	< 0.001	0.003	< 0.001	0.004
Oral calcimimetics (user)	β			0.175	0.106
	(*P*)			<0.001	0.032
IV calcimimetics (user)	β			0.094	
	(*P*)			0.034	

Independent variables in model 1; gender (male), age (years), dialysis vintage (years), DM (yes), serum corrected Ca (mg/dL), serum P (mg/dL), serum i-PTH (pg/mL), serum Alb (g/dL), and nPCR (g/kg/day). Independent variables in model 2; model 1 + oral calcimimetics (user), IV calcimimetics (user), oral VDRAs (user), and IV VDRAs (user)

burden from "oral calcimimetics" itself was 1.18 pills, resulting in an increase in the total pill burden. Second, because of higher serum P levels in users (5.53 ± 1.05 mg/dL vs. 5.25 ± 1.24 mg/dL in non-users, $P < 0.001$), more PBs were prescribed. Third, more Ca carbonate pills were prescribed to compensate for Ca-lowering effects of calcimimetics. Fourth, the patients prescribed calcimimetics may have had more comorbidities besides secondary hyperparathyroidism due to the longer dialysis vintage: 9.9 (5.0–16.0) years vs. 3.5 (1.6–6.8) years in non-users, $P < 0.001$. On the other hand, the pill burden from all PBs and from Ca-based PB was lower in oral VDRAs users compared with non-users. The pills of Ca carbonate constituted about half of all PBs. Therefore, it is considered that this result reflects that fewer Ca carbonate pills were prescribed to avoid hypercalcemia in oral VDRA users.

Our study had some limitations. First, this was a single-center study, and as such, it may be difficult to extrapolate our results to other institutions. However, 533 patients were included, which is higher than the number reported from other facilities [6, 8, 11, 12]. In addition, since the pill burden from PBs was almost the same as the result of DOPPS [9], the present results may be considered to represent the prescription status in other facilities in Japan. Second, the number of pills depends on the formulation of its preparation used in the facility. For example, a pill containing 500 mg of Ca carbonate is prescribed in our hospital, but this is counted as two pills in the facility where only the 250 mg formulation is used. Third, it is considered that the number of prescribed pills would be influenced by drug adherence, but it was not considered in this study. In a preliminary study, approximately 60–70% of patients at our facility showed good drug adherence. Therefore, this study is only based on the number of prescribed pills and not on the number of pills actually taken by patients. Lastly, gender, age, dialysis vintage, DM, serum Ca, P, i-PTH, Alb levels, and nPCR were variables in this study; however, other patient backgrounds were not investigated at all. Further analysis is needed, including comorbidities other than DM and other serum chemistries.

Conclusions

A high pill burden is more likely to occur in younger patients with longer dialysis vintage, DM, higher serum P levels, and prescription of calcimimetics. The present study also suggests a renewed focus on the importance of P management because PB was the single largest contributor to the total pill burden that positively and linearly correlated with serum P levels. It is necessary to demonstrate whether a high pill burden will be reduced by more efficient P management interventions.

Abbreviations

Alb: Albumin; Ca: Calcium; CKD-MBD: Chronic kidney disease-mineral and bone disorder; DM: Diabetes mellitus; DOPPS: Dialysis Outcomes and Practice Patterns Study; Fe: Iron; HCl: Hydrochloride; i-PTH: Intact parathyroid hormone; IV: Intravenous; La: Lanthanum; nPCR: Normalized protein catabolic rate; P: Phosphorus; PB: Phosphate binder; VDRA: Vitamin D receptor activator

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Authors' contributions

NN designed and performed the study, analyzed the data, and wrote the manuscript. KI and TT reviewed and revised the manuscript, and T Ogawa is

responsible for the final version of the manuscript. KI, YA, SM, HK, TA, and TT were responsible for the drug prescription for patients. T Ono contributed to the data of nPCR. KI, TA, and T Ogawa supervised the study. The authors read and approved the final version of this manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Hidaka Hospital Medical Ethics Committee (approval number: Heisei Hidaka Clinic 29). Consent to participate is not applicable.

Consent for publication
Not applicable.

Competing interests
NN has received consulting fees from Kyowa Kirin Co., Ltd (KK) and Sanwa Kagaku Kenkyusho Co., Ltd and lecture fees from KK, Nobelpharma Co., Ltd, Torii Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd (Ono), and Kissei Pharmaceutical Co., Ltd. T Ogawa has received grants (research support) from Takeda Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Ono, Mitsubishi Tanabe Pharma Co., Ltd, and Daiichi Sankyo Co., Ltd. The other authors declare that they have no competing interests.

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