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【 ORIGINAL ARTICLE 】

A Survey of Drug Burden in Patients Undergoing Maintenance Hemodialysis in Japan

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Abstract:

Objective This report presents a part of a survey pertaining to drug burden in maintenance hemodialysis patients in Japan.

Methods A patient-reported questionnaire-based survey was conducted from September to November 2016 in six regions in Japan.

Patients A total of 700 patients (50-79 years old) on maintenance hemodialysis for >3 years and members of the Japan Association of Kidney Disease Patients (JAKDP) were provided with the questionnaire. They were randomly selected using stratified sampling according to patient distribution observed from the Japanese Society for Dialysis Therapy Renal Data Registry (JSDT JRDR).

Results A total of 524 (74.9%) patient questionnaires were evaluated [mean (standard deviation; SD) age, 66.6 (7.2) years; males, 63.4%; dialysis vintage, 16.9 (9.1) years]. Patients' age, gender, and regional distribution were similar to the JSDT JRDR. They were taking an average (SD) of 16.4 (8.34) and 16.3 (8.55) oral medications/day on dialysis and nondialysis days, respectively. A majority of the patients were taking ≥ 10 oral medications/day on dialysis (75.1%) and nondialysis (74.4%) days, with phosphate binders being the most taken (7.0 tablets/day). A similar proportion (74.4%, 72.9%, respectively) was taking ≥6 different types of oral medications/day. Most patients were taking oral medications 3 (31%, 33%), 4 (24%, 22%), and ≥5 times (31%, 30%) a day, respectively. The drug burden was similar on dialysis and nondialysis days and did not vary with dialysis vintage.

Conclusion The number, type, and frequency of oral medications in maintenance hemodialysis patients are high in Japan. The proportion of phosphate binders was highest among the prescription medications.

Key words: drug burden, Japan, maintenance hemodialysis, patient-reported, questionnaire survey

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Introduction

Dialysis is an effective treatment strategy for end-stage kidney disease; however, additional treatment with a large number of medications is required to control the associated comorbid conditions and metabolic/mineral abnormalities (1); this includes chronic kidney disease (CKD)-mineral and bone disorders (CKD-MBD) (2). According to the December 2015 Annual Dialysis Data Report from the Japanese Society for Dialysis Therapy Renal Data Registry (JSDT JRDR), there were 39,462 new dialysis patients in 2015 among a total of 324,986 dialysis patients in Japan (3). The mean [standard deviation (SD)] age of dialysis initiation was 69.20 (13.39) years [men, 68.37 (13.26) years; women, 70.95 (13.48) years]. Almost half of the patients initiating dialysis had diabetic nephropathy (43.7%), and about one-third had glomerulonephritis (16.9%) or nephrosclerosis (14.2%). The most common causes of mortality among dialysis patients were heart failure (26%), infections (22.0%), and malignancy (9.3%). The combination of heart failure, cerebrovascular events, and myocardial infarction constituted 36.8% of the total reported deaths (3). Furthermore, a report by Iseki et al. (4) indicates a gradual increase in the number

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of chronic dialysis patients over the last decade from 2002 to 2012.

The associated CKD-MBD in this patient group is a systemic disorder presenting as abnormalities in the parathyroid hormone (PTH), calcium, phosphorus, and vitamin D metabolism (2, 5). Therefore, the CKD-MBD treatment guidelines specifically help achieve target levels of serum phosphorus, followed by calcium and PTH; this order of priority is set by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative™ guidelines (6, 7). It is now widely accepted that this dysregulated mineral metabolism in CKD not only results in bone disease but also increases vascular calcification, leading to an increased cardiovascular risk and a reduced survival (5, 8, 9). Other comorbid conditions and associated complications requiring treatment include diabetes, hypertension, renal anemia, and infectious disease (5, 10).

Therefore, the total drug burden in dialysis patients can be high; indeed, observational studies have reported that the median number and types of prescribed tablets per day can be as high as 19 and 12, respectively, more than for any other chronic disease (11, 12). Consequently, medication nonadherence within this group of patients is also high (13). Evidence also suggests that there may be differences in the drug burden between dialysis and nondialysis days. Data on the daily life experiences of patients on maintenance dialysis were obtained by evaluating the time spent on their activities, settings, and associated emotions in a study by Song et al. (14) and assessed using the Illness Effects Questionnaire-Self-Report (IEQ-S) and the Short-Form Health Survey-36v2 (SF-36v2); U-Index scores were also computed. The U-Index scores significantly differed between dialysis and nondialysis days for hemodialysis patients (p=0.012).

Although the dialysis vintage (length of time on dialysis) can be as high as 35 years (15) in Japan, limited data are available regarding the drug burden and treatment adherence in patients on maintenance dialysis (1). Furthermore, patients' expectations of treatment have also not been explored. Therefore, a questionnaire-based survey was conducted in this group of patients to evaluate aspects of drug burden, treatment adherence/compliance, and patient expectations. This report presents the part of the survey pertaining to drug burden in this specific patient group in Japan.

Materials and Methods

Survey objectives

The objective of this survey was to present information about the number, type, and frequency of oral medications taken by hemodialysis patients on days when there was dialysis (dialysis days) and days when there was no dialysis (nondialysis days) and when categorized by dialysis vintage. The patient demographics and characteristics were also compared to those of the hemodialysis patient population reported in the JSDT JRDR of December 31, 2014 (16).

Survey design and participants

A questionnaire-based survey was conducted from September to November 2016 in six regions in Japan: Hokkaido/Tohoku, Kanto, Chubu, Kinki, Chugoku/Shikoku, and Kyushu. The questionnaire was developed by Ono Pharmaceutical, under the guidance of the authors Dr. Masaki Ohya and Dr. Takashi Shigematsu, Department of Nephrology, Wakayama Medical University. The original questionnaire was in Japanese and was translated into English to conduct the analysis for this publication.

The survey was conducted in patients aged between 50 and 79 years who had been on maintenance hemodialysis for more than 3 years and were enrolled members of the Japan Association of Kidney Disease Patients (JAKDP). Patients on peritoneal dialysis or concomitant peritoneal dialysis and hemodialysis were excluded. Eligible patients were randomly selected from among the JAKDP members using stratified sampling according to the patient distribution (age and gender) observed in the JSDT JRDR. The number of patients to be enrolled from each prefecture was calculated by weighting as per the numbers of JAKDP members registered in each prefecture. Patient selection was done by the affiliations of the JAKDP settled in each prefecture. This survey was carried out by Wakayama Medical University in collaboration with Ono Pharmaceuticals and with the cooperation of the JAKDP. After patients had received an oral explanation of the survey by each branch of the JAKDP, their response to the question "Agree/Disagree" on the cover page of the questionnaire was considered the final consent; if a patient answered "disagree", he/she was still required to return the blank/empty anonymous survey form.

Seven hundred eligible patients were provided with the self-administered survey forms, sent via the JAKDP by post. Dialysis vintage was calculated as the period from the start of dialysis to the end/close of 2016 with durations of less than one year rounded down. Oral medication included tablets, capsules, powders, and liquid formulations; for the purpose of calculation, each dose was considered to be one tablet. The survey was approved by the ethics review board of Wakayama Medical University.

Survey questionnaire

The study questionnaire was provided to the eligible patients. The questionnaire was anonymous, identified only by a code number, and comprised 22 questions. The personal information of the patients was managed by the JAKDP; apart from patient age, no other identifiable patient data, such as the name or initials and date of birth, were accessible.

The survey questions were not open-ended and included multiple-choice answers relating to the number, type, and frequency of dosage of oral medications, comorbidities, dialysis vintage, handling of leftover medications, reasoning behind compliance, patient beliefs/expectations, and availability of information about treatment. In this report, we

Table. **Patient Characteristics.**

	Completed questionnaires (n=524)
Men/women, n (%)	332/182 (63.4/34.7)
Age, years, (mean±SD)	66.6±7.2
Dialysis vintage, years, (mean±SD)	16.9±9.1
Comorbidity, n (%)	
Hypertension	214 (40.8)
Cardiovascular disease	138 (26.3)
Diabetes	82 (15.6)
Dyslipidemia	15 (2.9)
Gastrointestinal disease	65 (12.4)
Respiratory disease	29 (5.5)
Cerebrovascular disease	32 (6.1)
Cancer	17 (3.2)
Others	76 (14.5)
Unknown	32 (6.1)

present the part of the survey pertaining to the number, type, and frequency of oral medications taken by hemodialysis patients on dialysis days, nondialysis days, and when stratified by dialysis vintage. The remaining survey results will be presented in a subsequent manuscript.

Assessments and statistical analyses

The demographic data of this study cohort, such as gender, age, dialysis vintage, and residential area, were compared with the dialysis patient population from the JRDR using descriptive statistics. In brief, the JRDR patient population represents the current status of chronic dialysis (including peritoneal dialysis) in Japan as of December 31, 2014. The registry survey targeted 4,367 dialysis facilities through electronic and partially paper-based surveys. Among these, responses were collected from 4,330 institutes; the survey recovery rate was 99.2% for institutes and 96.0% for patients (16). The number, type, and frequency of oral medications were compared between the dialysis and nondialysis days using descriptive statistics. The number, type, and frequency of oral medications were also stratified by dialysis vintage (3-5 years, 6-9 years, 10-14 years, 15-19 years, and ≥20 years) and evaluated using a one-way analysis of variance. Tukey's test was used for multiple comparisons. This comparison was made for both dialysis and nondialysis days. A significance level of 5% was used for all analyses, which were performed using the "BellCurve for Excel" software program (Social Survey Research Information, Tokyo, Japan).

Results

Demographic and baseline characteristics

Out of the 700 eligible patients who received the questionnaires, the responses from 524 (74.9%) were considered valid/complete for evaluation. The mean (SD) age of the respondents was 66.6 (7.2) years with a dialysis vintage of 16.9 (9.1) years, and the majority were men (63.4%). The most frequent comorbidities reported were hypertension (40.8%), cardiovascular disease (26.3%), diabetes (15.6%), and gastrointestinal disease (12.4%). Seventeen (3.2%) respondents had cancer (Table). The most common medication was phosphate binders, prescribed to 92.2% of the patients.

The age, gender, and regional distribution of the respondents were similar to those of the dialysis patient population reported in the December 31, 2014, JSDT JRDR. However, a greater proportion of the respondents had a longer dialysis vintage (≥10 years, 70.8%) than the patient population in the JRDR (≥10 years, 28%) (Fig. 1).

Number, type, and frequency of tablets

Patients were taking an average (SD) of 16.4 (8.34) and 16.3 (8.55) oral medications/tablets per day on dialysis and nondialysis days, respectively, and this number did not differ markedly between dialysis and nondialysis days (Fig. 2).

A majority of the patients (approximately 75%) were taking ≥10 oral medications/tablets per day, which also did not differ markedly between dialysis (75.1%) and nondialysis (74.4%) days. A similar proportion of the patients (approximately 73%) were taking ≥6 different types of oral medications/tablets per day, which did not differ markedly between dialysis (74.4%) and nondialysis (72.9%) days. Most patients were taking oral medications 3 times (31% and 33%), 4 times (24% and 22%), and ≥5 times (31% and 30%) a day, which again did not differ markedly between dialysis and nondialysis days (Fig. 3). The number, type, and frequency of oral medications did not significantly vary with dialysis vintage on dialysis or nondialysis days (Fig. 4).

Patients were questioned about the number of medications they were taking to reduce their phosphorus levels, to reduce their PTH levels, for hypertension, for diabetes, and as vitamin D preparations. Among these five different types of oral medications, patients took greater numbers of phosphate binders (7.0 tablets daily), followed by antihypertensive (2.8 tablets) and antidiabetic (2.0 tablets) medications (Fig. 5) than other medications.

Discussion

This is the first large-scale survey to investigate prescription drugs and actual conditions of administration for maintenance hemodialysis patients in Japan. The results of this survey show that the number, type, and frequency of oral medications taken by hemodialysis patients is high. The age, gender, and regional distribution of the respondents was a representative sample, as it was comparable to the dialysis patient population reported in the 2014 JRDR, with the exception that a greater proportion of patients had a relatively long dialysis vintage among the respondents (≥10 years, 70.8%) than in the JRDR (≥10 years, 28%) (16).

The assumption that there would be differences in the drug burden on dialysis and nondialysis days was not borne

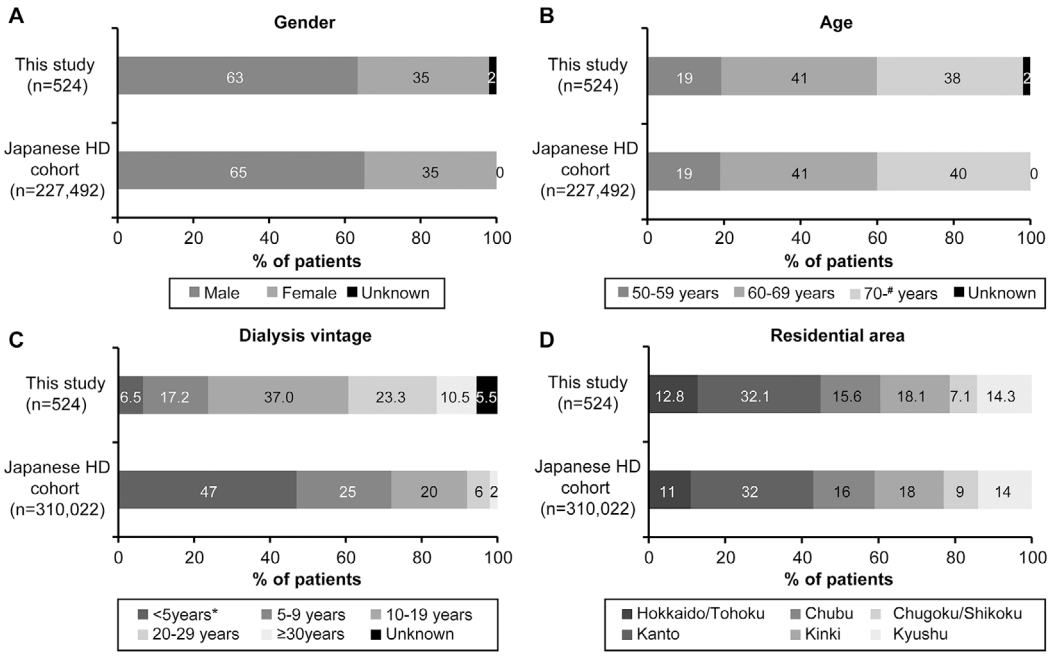

Figure 1. **A direct comparison of the current study cohort (members of JAKDP) with the dialysis patient population in the JSDT JRDR stratified by A) gender, B) age, C) dialysis vintage, and D) residential area. #Represents age range 70 to <80 years for this survey *Represents dialysis vintage 3 to <5 years for this survey. HD: hemodialysis, JAKDP: Japan Association of Kidney Disease Patients, JSDT JRDR: Japanese Society for Dialysis Therapy Renal Data Registry**

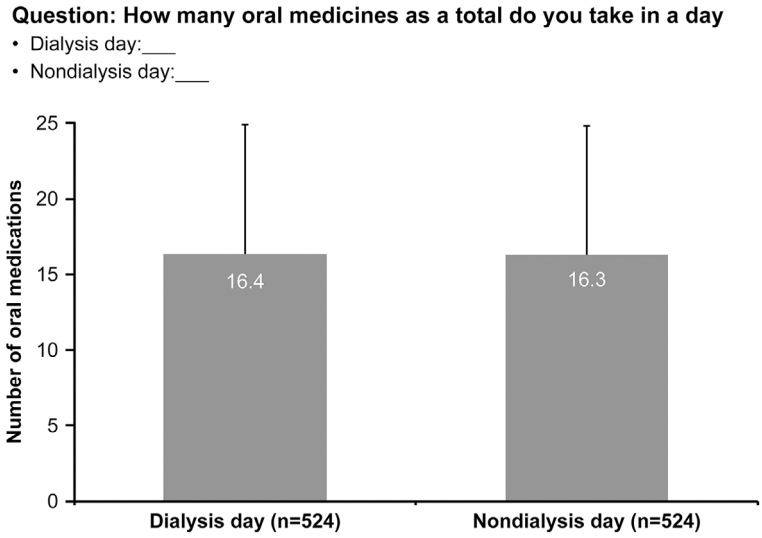

Figure 2. **Number of oral medications taken per day on dialysis and nondialysis days.**

out. The average number of medications taken per day was similarly high (n=16) on both dialysis and nondialysis days. A majority of the patients (approximately 75%) were taking ≥10 oral medications/tablets per day, which also did not differ markedly between dialysis and nondialysis days. These numbers were higher than those reported for 850 patients on chronic hemodialysis from Okinawa, Japan (7.2) in 2002 (1) and similar to those in the United States (median daily pill burden of 19) and were associated with a low health-related quality of life (11).

However, in Japan, no guidelines for secondary parathyroidism or CKD-MBD had been established in 2002. Physicians could prescribe only oral or intravenous vitamin D products, with calcium carbonate as the sole available phosphate binder. Given that the use of drugs for CKD-MBD management has been recently established in the last decade (5), a new survey was performed.

Another reason for the high pill burden observed was an increase in the availability of novel phosphate binders and oral antidiabetics for dialysis patients, based on the findings of both the Tozawa et al. and Chiu et al. studies (1, 11). While the increase in the use of phosphate binders is likely

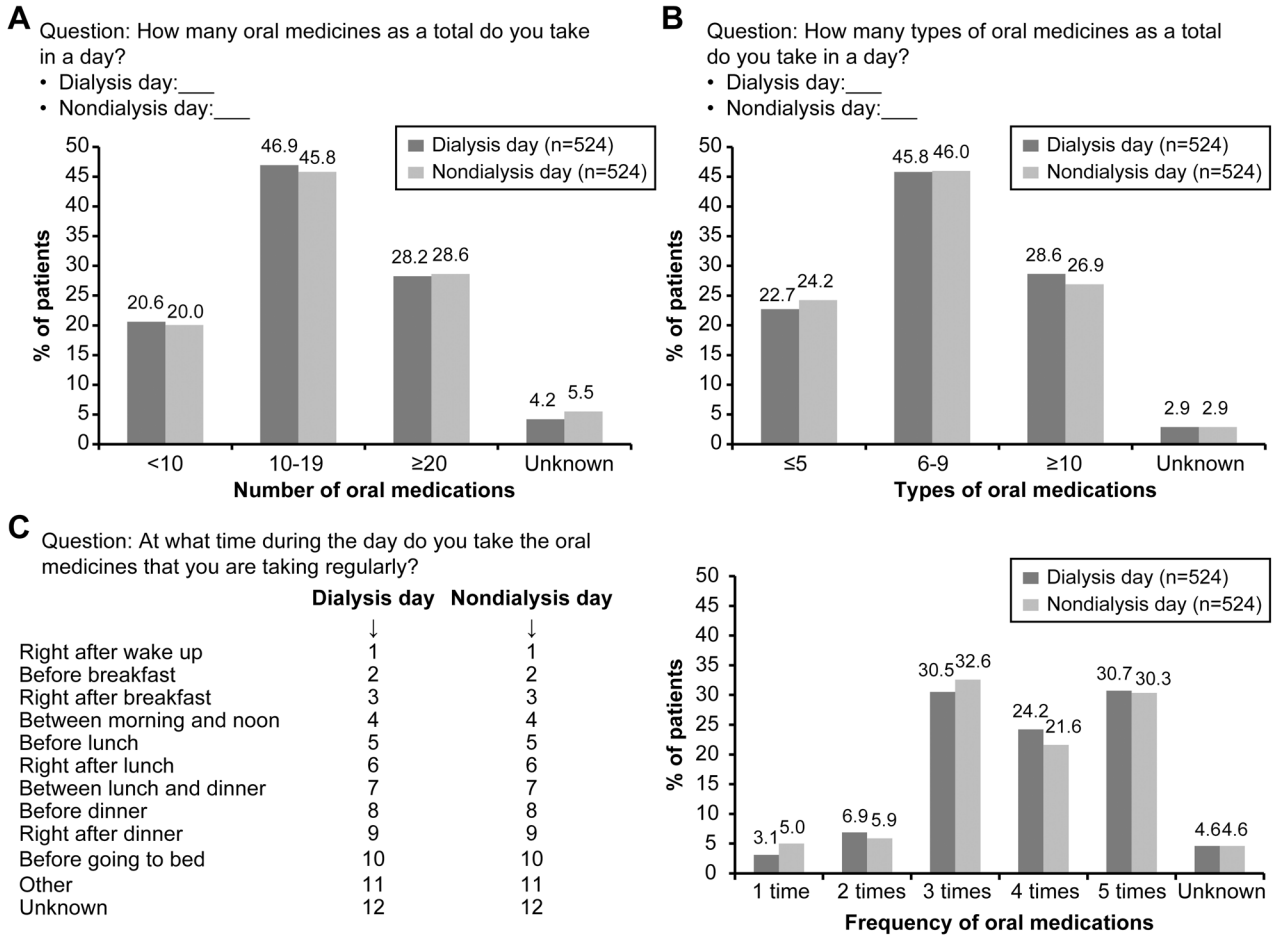

Figure 3. **Proportion of patients categorized by (A) number, (B) types, and (C) frequency of oral medications taken per day on dialysis and nondialysis days.**

to be due to the current guidelines introduced in the last decade (5), the use of oral antidiabetics is related to the association between end-stage renal disease and diabetic nephropathy (17).

A similar proportion of patients (approximately 73%) was taking ≥6 different types of oral medications/tablets per day. These numbers were higher than the average number of medication types per external prescription (approximately 2.9) or that for people 50-79 years of age (approximately 3-4) in Japan, as published by the Ministry of Health, Labour and Welfare in 2015 (18). Furthermore, the proportion of patients taking ≥6 medication types in this study was higher than that in the Japanese elderly population (29% for those having ≥2 chronic diseases; 47% for those diagnosed with dementia) (18). These results suggest that patients on dialysis take a higher number of different medication types than the general population in Japan, although differences in the data collection measures should be noted (patient-reported vs. prescription data-based).

Most patients were taking oral medications 3 times (approximately 31%), 4 times (approximately 23%), and ≥5 times (approximately 30%) a day, which again did not differ markedly between dialysis and nondialysis days. The number, type, and frequency of oral medications did not significantly vary with dialysis vintage on dialysis or nondialysis days. Among the five different types of oral medications assessed, the highest average number that the patients were taking per day was for phosphate binders (7.0 tablets), followed by antihypertensive (2.8 tablets) and antidiabetic (2.0 tablets) medications.

These findings were similar to those obtained in the cross-sectional multicenter survey from Okinawa, Japan, in August 1999, where the three drug types most often prescribed to patients on hemodialysis were those related to calcium and phosphate metabolism (88%), antihypertensive agents (71%), and erythropoietin (60%) (1). Phosphate binders also accounted for about half of the daily pill burden in 233 patients undergoing chronic dialysis from three units in different geographic areas in the United States (11).

The Japanese guideline uses a treatment algorithm for serum PTH regulation based on the control of the serum phosphorus and calcium levels. Serum concentrations of phosphorus, corrected calcium, and PTH are maintained within the defined target ranges, and control of serum phosphorus should have the highest priority, followed by that of calcium and then that of PTH (5). These target ranges for serum phosphorus, calcium, and PTH in the guideline are based on survival data of Japanese dialysis patients. Given that Japa-

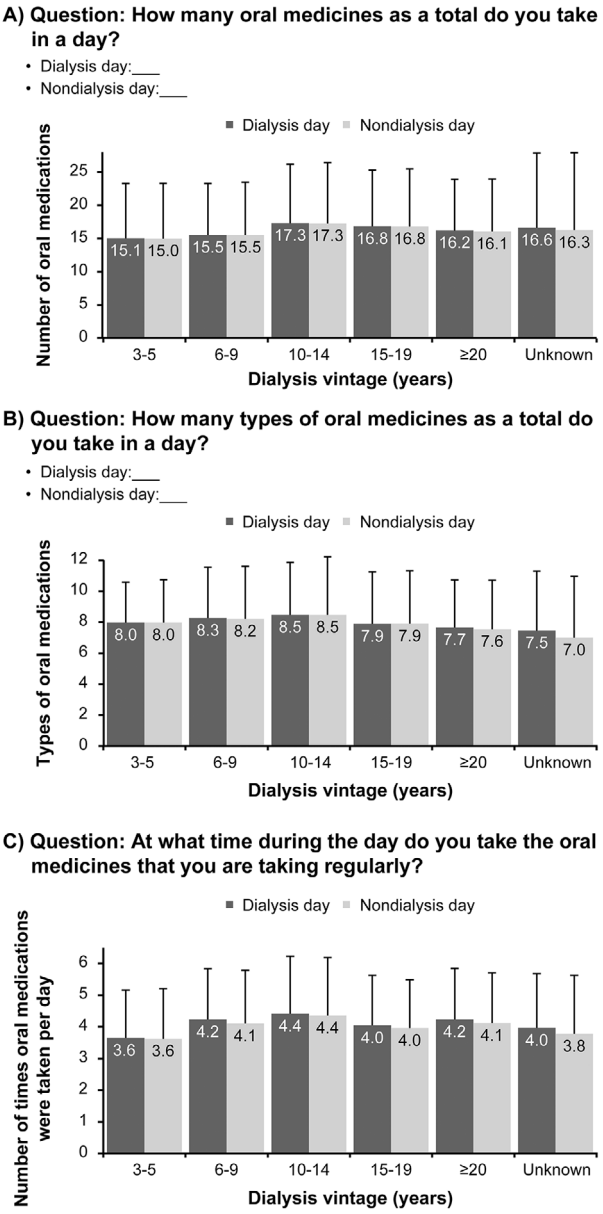

Figure 4. **Oral medication (A) number, (B) types, and (C) frequency categorized by dialysis vintage of the patients.**

nese dialysis patients tend to have a longer dialysis vintage than their American and European counterparts, parathyroid control should be initiated at an early stage of CKD in this patient population (7). Furthermore, circulating phosphorus and calcium levels contribute to the life prognosis and appear to be more significant to this end than the effects of the parathyroid function (19). Evidence from randomized clinical trials suggests that no single treatment intervention is likely to reduce the high mortality risk in dialysis patients; however, several robust secondary analyses indicate potential benefits of controlling CKD-MBD-related factors and secondary hyperparathyroidism (20-24).

This understanding of the treatment algorithm is also reflected in the results of this survey. Phosphorous binders were the most frequently taken drugs and were administered in nearly all patients (92.2%). The main cause of CKD-MBD is believed to be hyperphosphatemia, and in patients undergoing dialysis, elevated serum phosphorus is also associated with secondary hyperparathyroidism and cardiovascular disease and most importantly with cardiovascular mortality (19); therefore, phosphate binders are expected to have a high administration rate (5, 7). In addition, the administration frequency of phosphate binders is considered to be one of the reasons for the high number of doses and increased daily frequency and is directly proportional to the number of meals, irrespective of when they were taken. Similarly, vitamin D receptor activation therapy is an important intervention for CKD-MBD treatment to reduce the risk of developing cardiovascular disease and improve the vital prognosis, even with low serum intact PTH levels (25); however, this treatment is only available in an injectable formulation, which results in a lower administration rate than might be seen with an oral formulation. Finally, approximately 50% of patients are taking calcimimetic medication for secondary hyperparathyroidism, indicating that this is gaining acceptance as a major therapeutic intervention tool for CKD-MBD (20).

Some limitations associated with this study included the

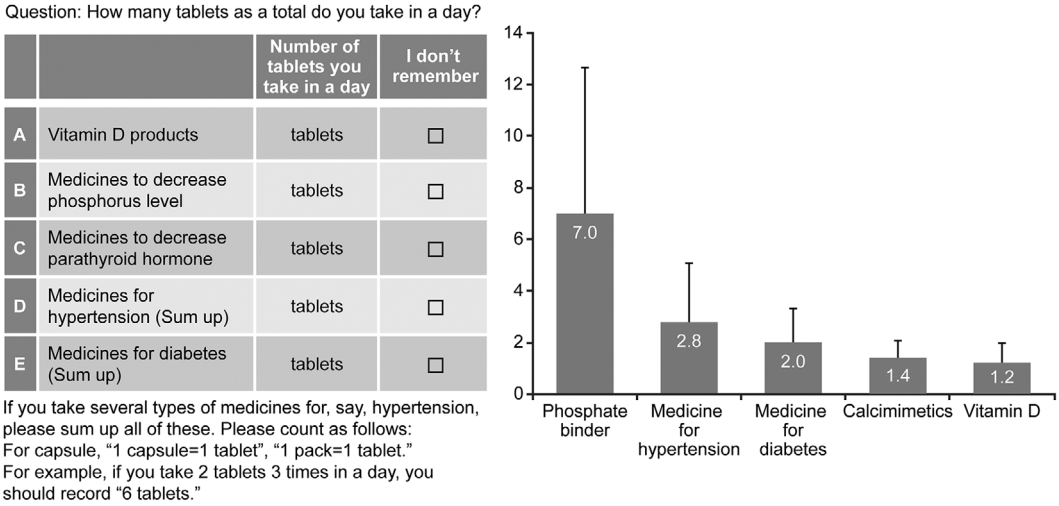

Figure 5. **The number of types of oral medications taken per day.**

fact that the survey questions assumed that the medications taken were those prescribed. Furthermore, patients were questioned regarding the number of medications for five different types of oral medications only (to reduce phosphorus levels, to reduce PTH levels, for hypertension, for diabetes, and as vitamin D preparations). As the patients were randomly selected from among those who enrolled in the patients' association (JAKDP), instead of the entire population in Japan, a selection bias cannot be ruled out. Finally, for this survey, the comparison with the JRDR data for the dialysis vintage was restricted to a vintage between 3 and <5 years, and the age range was restricted to <80 years. Despite these limitations, we still opted to use a patient-reported approach in order to simplify the questionnaire for ease of understanding.

Overall, given the drug burden in this population, it is imperative for clinicians to adjust the dosage appropriately based on the renal function and give consideration to potential drug-drug interactions.

Conclusion

The results of the survey showed that the number, type, and frequency of oral medications in maintenance hemodialysis patients are high in Japan. The proportion of medications used to treat CKD-MBD, specifically phosphate binders, was the highest among all the prescription medications.

Author's disclosure of potential Conflicts of Interest (COI).
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