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Increased risk of hypocalcemia with decreased kidney function in patients prescribed bisphosphonates based on real-world data from the MID-NET® in Japan: a new-user cohort study

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Abstract

Background In the post-marketing stage, cases of hypocalcemia associated with bisphosphonate preparations (BPs) have been reported in patients with decreased kidney function, despite warning against use of BPs in such patients in the package insert (PI) of Japan. The purpose of this study was to investigate the safety of BPs in patients with decreased kidney function.

Methods The cohort study was conducted in patients with osteoporosis and newly prescribed bisphosphonate utilizing real-world data from MID-NET® in Japan. The adjusted hazard ratios (aHRs) for hypocalcemia (a corrected serum Ca level < 8.00 mg/dL) relative to the normal group were calculated in each decreased kidney function group (mild, moderate or severe group).

Results A total of 14,551 patients were included in the analysis, comprising 2,601 (17.88%) with normal (eGFR ≥ 90 mL/min/1.73m^2), 7,613 (52.32%) with mild (60 ≤ eGFR < 90 mL/min/1.73m^2), 3,919 (26.93%) with moderate (30 ≤ eGFR < 60 mL/min/1.73m^2), and 418 (2.87%) with severe kidney function (eGFR < 30 mL/min/1.73m^2). The aHRs (95% confidence interval) for hypocalcemia were 1.85 (0.75–4.57), 2.30 (0.86–6.21), and 22.74 (8.37–61.78) in the mild, moderate, and severe groups, respectively. The increased risk of hypocalcemia depending on kidney function was also observed even when calculating the aHR for each specific BP such as alendronate sodium hydrate, minodronic acid hydrate, and sodium risedronate hydrate. Furthermore, similar results were obtained in the sensitivity analysis by altering the outcome definition to a 20% or more reduction in corrected serum Ca level from the baseline, as well as when focusing on patients with more than one laboratory test result per 30 days during the follow-up period.

Conclusions These findings suggest that the risk of hypocalcemia during BP prescription is higher in patients with decreased kidney function, particularly those with severely decreased kidney function. The quantitative

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real-world evidence on the safety risk of BPs obtained in this study has led to the PI revision describing a relationship between hypocalcemia risk and decreased kidney function as a regulatory action in Japan and will contribute to promoting the proper use of BPs with appropriate risk management in clinical practice.

Keywords Bisphosphonates, Hypocalcemia, Renal impairment, Pharmacoepidemiology, Real-world evidence

Background

Bisphosphonate preparations (BPs) are widely used as the first-line drug for osteoporosis other than early postmenopausal osteoporosis [1–3]. Actually, the use of BPs in patients with severely decreased kidney function has been alerted in the package insert (PI) on the "Contraindications" section of etidronate disodium [4], sodium risedronate hydrate [5, 6], and zoledronic acid hydrate [7], and on the "Precautions Concerning Patients with Specific Backgrounds" section of many BPs [8]. This precautionary stance arises from the absence of clinical BP use in such patients and potentially increased risk inferred from the renal excretion pathway of BPs [9]. Additionally, hypocalcemia is known as an adverse reaction of BPs [9–12] and precaution for hypocalcemia was commonly included in the PI for BPs except etidronate disodium [4–8], although no information about a relationship between hypocalcemia risk and decreased kidney function was included.

Regarding the situation at post-marketing in Japan, results in drug use surveys and spontaneous adverse reaction reports indicate instances of hypocalcemia during BPs administration in patients with decreased kidney function [13]. It suggests the prescription of BPs to patients with decreased kidney function even in the absence of quantitative safety information regarding BPs in clinical practice in Japan.

Consequently, the Pharmaceuticals and Medical Devices Agency (PMDA) has decided to undertake a pharmacoepidemiological study to comprehend the safety characteristics of BPs in patients with decreased kidney function based on the risk of hypocalcemia as an indicator within a real-world setting.

Methods

Database

Real-world data from MID-NET®, a reliable and valuable database in Japan [14, 15], were used for analysis in this study because MID-NET® stores electronic medical records, administrative claim data, and diagnosis procedure combination (DPC) data for over 6.05 million patients (as of December 2022) in cooperation with 10 healthcare organizations, including 23 university hospitals and regional core hospitals. The study period spanned from January 1, 2009, to March 31, 2019.

Utilizing MID-NET® for this study was approved on February 19, 2020, through a discussion by the expert committee of MID-NET® [16] and the actual data extraction from MID-NET® for analysis was carried out in the week of May 22, 2020.

Cohort and study design

In this study, a new-user cohort design was selected for considering the degree of renal dysfunction and abnormal serum calcium (Ca) levels after BP administration. Specifically, as shown in Fig. 1, patients who met all of the following conditions were included in this study; 1) patients prescribed BPs targeted in this study during the study period, 2) patients with a record of an osteoporosis-related diagnosis in the same month as t_0 (the earliest prescription date of BPs), 3) patients with initial medical records at least 90 days before t_0, and 4) patients with a record of serum creatinine (Cr) or estimated glomerular filtration rate (eGFR) from 90 days before t_0 to the day before t_0 (baseline period). For the analysis, patients who met one or more of the following criteria were excluded to select an appropriate population without a higher risk of hypocalcemia; 1) patients prescribed multiple BPs at t_0, 2) patients with a record of corrected serum Ca level < 8.00 mg/dL during the baseline period, 3) patients with a record of an episode of primary hyperparathyroidism during the baseline period, 4) patients prescribed denosumab (genetical recombination) at least once during and after the baseline period, 5) patients with a record of an episode of acute pancreatitis or sepsis during and after the baseline period, and 6) patients prescribed at least one dose of asfotase alfa (genetical recombination), cinacalcet hydrochloride, evocalcet, or etelcalcetide hydrochloride during and after the baseline period (see Additional file 1 for more details of this study design).

The target BPs in this study included all BPs (not only oral preparations but also intravenous preparations) with an indication for osteoporosis marketed in Japan during the study period; i.e., alendronate sodium hydrate, etidronate disodium, ibandronate sodium hydrate, minodronic acid hydrate, sodium risedronate hydrate, and zoledronic acid hydrate.

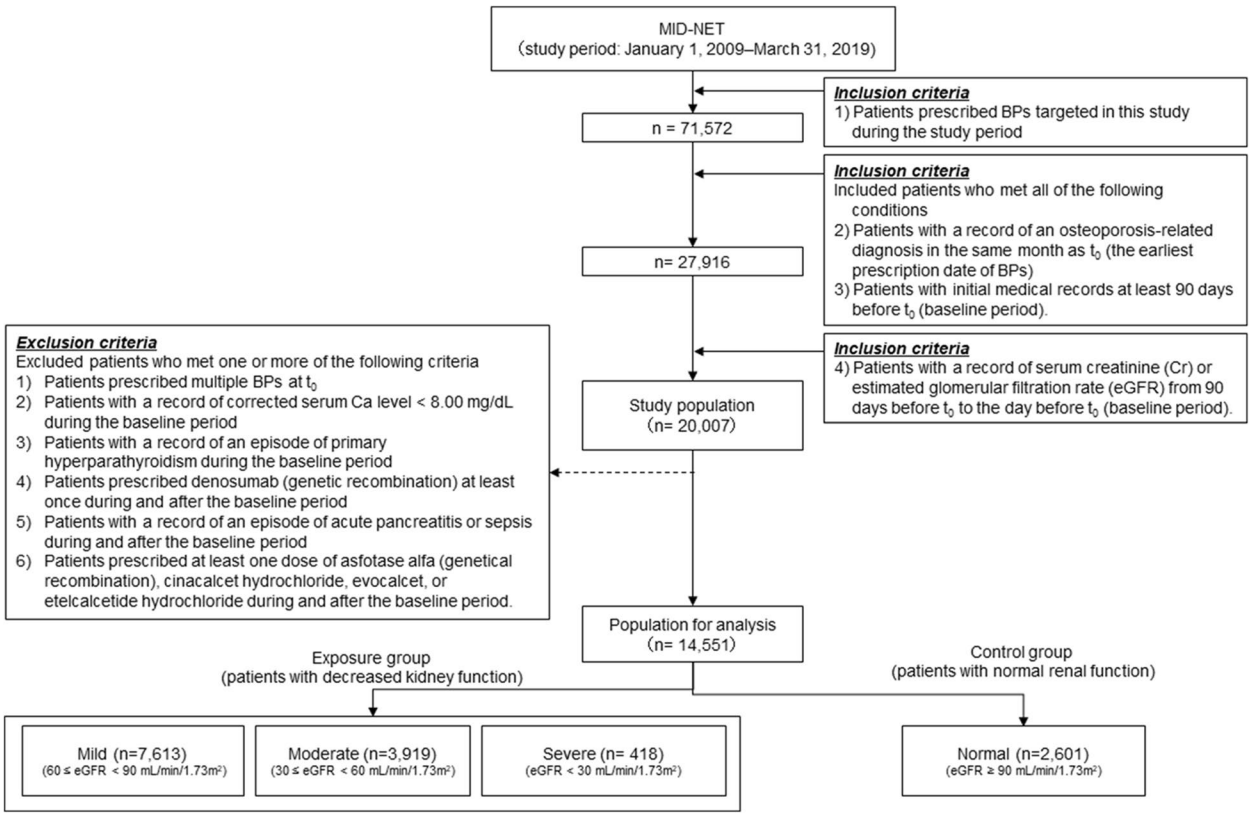

Fig. 1 Flow chart for patient selection

Definition of exposure

In order to evaluate the relationship between the incidence of hypocalcemia and decreased renal function, renal function was stratified into four categories based on eGFR value: normal (eGFR $\geq$ 90 mL/min/1.73m^2), mild (60 mL/min/1.73m^2 $\leq$ eGFR < 90 mL/min/1.73m^2), moderate (30 mL/min/1.73m^2 $\leq$ eGFR < 60 mL/min/1.73m^2), severe (eGFR < 30 mL/min/1.73m^2). In cases where eGFR values were not recorded, the values were calculated from serum Cr values using the following formula widely used in Japan [17, 18]: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for women) (mL/min/1.73m^2). In instances where multiple eGFR values were available on the same day, the mean eGFR value was used. The baseline eGFR value was determined as the mean of the two eGFR values closest to t_0 during the baseline period. If only one examination was performed during the baseline period, that single value was used as the baseline eGFR. No data imputations for missing values were made in calculating eGFR.

Definition of prescription and follow-up periods

The prescription period encompassed the start date (t_0) and duration of the prescription with a gap and a grace period, in consideration of prescription interval for each BP and a deviation from the scheduled visit time, etc. The gap and the grace periods were equally set based on the information in the PI; i.e., 14 days for BPs prescribed either once a week or once a day, 56 days for BPs prescribed once every 4 weeks, 60 days for BPs prescribed once a month, and 90 days for BPs prescribed once a year. Consequently, two prescriptions for the same drug were considered continuous if the latter prescription date fell within the gap period of the former prescription date.

The follow-up period commenced at t_0 and concluded at the earliest date of the following; 1) the end date of the prescription period, 2) the day before the start date of another different BP prescription from t_0, 3) the date of changing renal function category defined as the second date of two consecutive changes of a different category from the baseline, or 4) the end date of the study period (March 31, 2019).

Definition of outcome

"Hypocalcemia" was defined as a corrected serum Ca level < 8.00 mg/dL, as per Payne's equation, a widely employed method in Japan [19, 20]. If multiple values were recorded on the same day, the minimum serum Ca value and the maximum albumin (Alb) value were used. To determine the corrected serum calcium level, the serum Alb value measured within 14 days of the serum Ca measurement was selected, with preference given to the value closest to the date of serum Ca measurement. No data imputations for missing values were made in calculating serum Ca value.

Definition of covariates

The covariates used in this study included gender (male/female), age (age < 65 years, 65 years to < 75 years, 75 years and older), and complications (hypoparathyroidism, vitamin D deficiency, magnesium disorders) as well as concomitant drugs (elcatonin, steroids excluding topical preparations, calcium preparations excluding topical preparations, vitamin D preparations excluding topical preparations, sorafenib tosilate, lenvatinib mesilate, vandetanib, enviomycin sulfate, and monobasic sodium phosphate monohydrate/dibasic sodium phosphate anhydrous) among diseases and drugs known to be associated with the risk of hypocalcemia [8, 21, 22]. Data at t_0 for sex and age, and at the baseline period for complications and concomitant drugs were used for analysis.

Statistical analysis

Patient background data, including covariates, each active ingredient of BPs at t_0, concomitant drugs known to cause osteoporosis during the follow-up period, and the calendar year of t_0 were tabulated.

The incidence rate of hypocalcemia (/patient-year) in each group, the crude hazard ratio (cHR) and adjusted hazard ratio (aHR; with adjustment for the covariates described above) of each group to the normal group (Cox proportional hazards model) were calculated. These analyses were also performed for each active ingredient of BPs at t_0.

In addition, sensitivity analysis was conducted by changing the outcome definition from "corrected serum Ca level < 8.00 mg/dL" in the primary analysis to "20% or more reduction of corrected serum Ca level from the baseline." The baseline serum Ca level was defined as the value closest to t_0 among the corrected serum Ca values in the baseline period. Furthermore, to check the impacts of the lack of laboratory tests during the BP prescription period, the same analysis as the primary was conducted only in patients with more than one laboratory test result per 30 days during the follow-up period. In this population, the median (first quartile, third quartile) frequency for laboratory tests was 1.7 (1.4, 3.2) for the normal, 1.5 (1.4, 3.2) for the mild, 1.8 (1.4, 3.8) for the moderate, and 2.2 (1.4, 5.6) for the severe groups. The aHRs were also calculated when dialysis patients who had a record of dialysis before t_0 were excluded from the cohort of the primary analysis.

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analysis.

Results

Cohort

During the study period, 71,572 patients were prescribed BPs targeted in this study. Of those, 14,551 patients were included for analysis after applying all inclusion and exclusion criteria (Fig. 1). The number of patients in each group was 2,601 (17.88%) for the normal, 7,613 (52.32%) for the mild, 3,919 (26.93%) for the moderate, and 418 (2.87%) for the severe groups.

The patient backgrounds are summarized in Table 1. No major differences among the groups were observed, except for a higher proportion of elderly patients in the moderate and severe groups, and greater number of steroid prescription in the normal group. The most frequently prescribed BP in this study was alendronate sodium hydrate (53.44–64.59%), followed by sodium risedronate hydrate (19.62–30.03%) and minodronic acid hydrate (14.35–16.77%).

Risk comparison of hypocalcemia among patients with different categories of decreased kidney functions

As shown in Fig. 2, the incidence rates of hypocalcemia (corrected serum Ca level < 8.00 mg/dL) were approximately 0.01 for the mild and moderate groups and 0.161 for the severe group. The aHRs (95% confidence interval (CI)) for hypocalcemia relative to the normal group were 1.85 (0.75–4.57), 2.30 (0.86–6.21), and 22.74 (8.37–61.78) in the mild, moderate, and severe groups, respectively. Importantly, the aHR demonstrated a consistent increase in declining kidney function, and the increased risk observed in the severe group was statistically significant. The median time from t_0 to cause hypocalcemia was 15 days with the first-third quartiles of 6–43 days with similar distribution in all groups.

The increased risk of hypocalcemia (corrected serum Ca level < 8.00 mg/dL) depending on kidney function was also observed even when calculating aHR for each BP. For example, aHRs (95% CI) in the severe group were 16.03 (4.68–54.96) for alendronate sodium hydrate, 40.21 (3.75–430.64) for minodronic acid hydrate, and 23.03 (1.89–280.35) for sodium risedronate hydrate, although no cases of hypocalcemia in the severe group were

Table 1 Patients backgrounds

	Control		Exposure					
	Normal n=2601 (number, %)		Mild n=7613 (number, %)		Moderate n=3919 (number, %)		Severe n=418 (number, %)	
Sex [a]								
Male	819	31.49	2056	27.01	1233	31.46	124	29.67
Female	1782	68.51	5557	72.99	2686	68.54	294	70.33
Age [a]								
mean (± standard deviation)	54.9	(±19.2)	67	(±13.8)	73.6	(±12.3)	74.1	(±13.1)
median (first quartile, third quartile)	59	(40,70)	70	(60,77)	76	(68,82)	76	(68,83)
Age group [a]								
0–64	1584	60.90	2627	34.51	670	17.10	73	17.46
65–74	627	24.11	2498	32.81	1062	27.10	99	23.68
75 and older	390	14.99	2488	32.68	2187	55.81	246	58.85
Year of t_0								
2009	92	3.54	245	3.22	103	2.63	<10 [f]	<2.39 [f]
2010	205	7.88	532	6.99	241	6.15	28	6.70
2011	223	8.57	532	6.99	253	6.46	30	7.18
2012	261	10.03	670	8.80	360	9.19	50	11.96
2013	256	9.84	825	10.84	389	9.93	35	8.37
2014	307	11.80	848	11.14	452	11.53	41	9.81
2015	269	10.34	829	10.89	466	11.89	54	12.92
2016	293	11.26	905	11.89	495	12.63	45	10.77
2017	285	10.96	999	13.12	493	12.58	49	11.72
2018	341	13.11	983	12.91	538	13.73	62	14.83
2019	69	2.65	245	3.22	129	3.29	<24 [f]	<5.74 [f]
Prescribed bisphosphonate preparation [a]								
alendronate sodium hydrate	1390	53.44	4120	54.12	2192	55.93	270	64.59
etidronate disodium	<18 [f]	<0.69 [f]	11	0.14	<10 [f]	<0.26 [f]	0	0.00
ibandronate sodium hydrate	25	0.96	56	0.74	34	0.87	<10 [f]	<2.39 [f]
minodronic acid hydrate	387	14.88	1277	16.77	608	15.51	60	14.35
sodium risedronate hydrate	781	30.03	2098	27.56	1050	26.79	82	19.62
zoledronic acid hydrate	<10 [f]	<0.38 [f]	51	0.67	<35 [f]	<0.89 [f]	<10 [f]	<2.39 [f]
Complications during the baseline period								
hypoparathyroidism [b]	11	0.42	33	0.43	<10 [f]	<0.26 [f]	<10 [f]	<2.39 [f]
vitamin D deficiency [c]	51	1.96	125	1.64	50	1.28	<10 [f]	<2.39 [f]
magnesium disorders [d]	12	0.46	35	0.46	26	0.66	<10 [f]	<2.39 [f]
Concomitant drugs during the baseline period								
elcatonin	18	0.69	61	0.80	46	1.17	11	2.63
steroids [e]	1411	54.25	3209	42.15	1534	39.14	151	36.12
calcium preparations [e]	50	1.92	147	1.93	97	2.48	15	3.59
vitamin D preparations [e]	398	1.53	1032	13.56	592	15.11	78	18.66
sorafenib tosilate	<10 [f]	<0.38 [f]	<10 [f]	<0.13 [f]	<10 [f]	<0.26 [f]	<10 [f]	<2.39 [f]
lenvatinib mesilate	0	0.00	<10 [f]	<0.13 [f]	0	0.00	0	0.00
vandetanib	0	0.00	0	0.00	0	0.00	0	0.00
enviomycin sulfate	0	0.00	0	0.00	0	0.00	0	0.00
monobasic sodium phosphate monohydrate /dibasic sodium phosphate anhydrous	<10 [f]	<0.38 [f]	<10 [f]	<0.13 [f]	<10 [f]	<0.26 [f]	<10 [f]	<2.39 [f]
Concomitant drugs prescribed during the follow-up period								
steroids [e]	1666	64.05	3788	49.76	1836	46.85	186	44.50
methotrexate	226	8.69	554	7.28	143	3.65	<10 [f]	<2.39 [f]
heparin [e]	290	11.15	573	7.53	387	9.87	63	15.07
warfarin	76	2.92	226	2.97	269	6.86	43	10.29
anticonvulsants(hydantoin and barbiturate)	18	0.69	25	0.33	12	0.31	<10 [f]	<2.39 [f]
lithium preparations	<10 [f]	<0.38 [f]	<10 [f]	<0.13 [f]	<10 [f]	<0.26 [f]	0	0.00
gonadotropin-releasing hormone agonist	12	0.46	79	1.04	58	1.48	<10 [f]	<2.39 [f]
tamoxifen	<10 [f]	<0.38 [f]	28	0.37	<10 [f]	<0.26 [f]	<10 [f]	<2.39 [f]
aromatase inhibitor	66	2.54	269	3.53	71	1.81	<10 [f]	<2.39 [f]

Table 1 (continued)

[a] at t_0

[b] defined based on ICD-10 codes of E200, E201, E208, E209 and E892

[c] defined based on ICD-10 codes of E550, E559 and M8339

[d] defined based on ICD-10 codes of E612, E834, R790 and T568

[e] Excluding topical preparations

[f] When the number of patients was < 10, an aggregated value was presented based on the MID-NET® publication rule, so that the specific number could not be identified

category	Number of patients	Follow-up period (patient-year)	Number of cases [a]	Incidence rate (/patient-year) [a]	95 % CI	cHR [b]	95 % CI	aHR [b]	95 % CI
Normal	2601	755.01	<10	<0.013		1		1	
Mild	7613	2826.23	27	0.010	0.006 - 0.014	1.44	0.59 - 3.49	1.85	0.75 - 4.57
Moderate	3919	1374.43	16	0.012	0.006 - 0.018	1.69	0.66 - 4.31	2.30	0.86 - 6.21
Severe	418	99.57	16	0.161	0.082 - 0.240	18.60	7.27 - 47.54	22.74	8.37 - 61.78

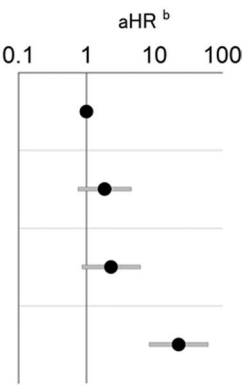

Fig. 2 Hazard ratios for hypocalcemia in each group of decreased kidney function (vs normal group). aHR: adjusted hazard ratio, cHR: crude hazard ratio, CI: confidence interval. [a]When the number of patients was < 10, an aggregated value was presented based on the MID-NET® publication rule, so that a specific number could not be identified. [b]aHR and cHR were calculated based on the Cox proportional hazards model and aHR was adjusted with the covariates (see "Methods")

observed for other BPs due to the limited sample size (see Additional file 2 for other aHRs of each BP).

In the sensitivity analysis by changing the outcome definition to 20% or more reduction in corrected serum Ca level from the baseline, the aHRs (95% CI) (vs normal group, $n = 1{,}848$) were 0.67 (0.16–2.86) for the mild ($n = 5{,}225$), 2.25 (0.57–8.94) for the moderate ($n = 2{,}700$), and 22.89 (5.87–89.21) for the severe ($n = 338$) groups. It should be noted that 4,440 patients in the cohort were excluded for this analysis due to unavailability of serum Ca level during the baseline period.

Additionally, on the analysis targeted only for patients with more than one laboratory test result per 30 days during the follow-up period, the aHRs (95% CI) (vs normal group, $n = 818$) were 2.20 (0.83–5.85) for the mild ($n = 1{,}982$), 1.95 (0.68–5.61) for the moderate ($n = 1{,}224$), and 11.34 (3.97–32.36) for the severe ($n = 217$) groups. Furthermore, when dialysis patients were excluded, the aHRs (95% CI) (vs normal group, $n < 2{,}601$) were 1.81 (0.73–4.49) for the mild ($n = 7{,}599$), 2.10 (0.77–5.72) for the moderate ($n = 3{,}899$), and 21.36 (7.75–58.85) for the severe ($n = 397$) groups.

Discussion

This study examined the characteristics of hypocalcemia during BP prescription. The incidence of hypocalcemia observed in this study was generally low and comparable to the percentage (less than a few percentage; ~ 5%) in the PI of BPs in Japan. BP prescription to patients with severely decreased kidney function have not been generally recommended because of insufficient safety data and the potentially increased risk of adverse events, such as hypocalcemia in these patients [2, 23, 24]. This study provides quantitative data regarding the increased risk of hypocalcemia in patients with decreased kidney function who were prescribed BPs. The magnitude of the increased risk during BP prescription was correlated with the degree of decreased kidney function, with a notably higher risk observed in patients with severely decreased kidney function. The increased risk in the severe group was substantiated by the results of sensitivity analysis where the outcome definition was changed to "20% or more reduction of corrected serum Ca level from the baseline."

In addition, the similar increased risks of hypocalcemia depending on kidney function were also observed when analyzing only patients with more than one laboratory test result per 30 days during the follow-up period. This

result suggests that the increased risk was associated with decreased kidney function rather than variations in the frequency of laboratory tests for serum Ca levels among the groups, such as more frequent in the severe group and less frequent in the normal, the mild or moderate groups. The presence of dialysis patients did not also significantly affect the study results, because the similar increased risks to the primary analysis were observed even when dialysis patients were excluded from the analysis. Differences in patient backgrounds among the groups were also unlikely to affect the results, because at least the backgrounds between the moderate and severe groups were similar including age distribution and the percentage of steroid prescription.

Furthermore, similar increased risk of hypocalcemia was identified across different BPs, such as alendronate sodium hydrate, minodronic acid hydrate, and sodium risedronate hydrate. These results suggest that the increased risk of hypocalcemia may be a common characteristic of BPs, supported by their shared pharmacological action of inhibiting bone resorption through osteoclast apoptosis [9]. Recent report also highlight a higher risk of hypocalcemia in patients with decreased kidney function prescribed denosumab or bisphosphonate [25]. Our finding supports those results through pharmacoepidemiological methods analyzing real-world data. The reason for different incidence of hypocalcemia between the studies could be due to the study condition and different data source including different definition of hypocalcemia and different target of BPs (all preparations in our study vs. only oral preparation in the other study, etc.).

As described above, this study delivered real-world evidence regarding the increased risk of hypocalcemia during BP prescription that is useful in clinical practice for promoting proper use of BPs with appropriate risk management.

The strength of this study was the utilization of longitudinal laboratory test results of serum Ca as an outcome of hypocalcemia from MID-NET®, a reliable database [14, 15]. However, as a limitation, results may be affected by severity of decreased kidney function itself [26] as well as other potential confounders such as changes of parathyroid function [21, 22] during the follow-up period, a severity of complications other than kidney function and other concomitant drugs not adjusted in this study.

Building on the findings of this study and other relevant information, including case reports and related literature, the safety assessment by the PMDA prompted the Ministry of Health, Labour and Welfare to revise the PI of BPs in January 2023. In this revision more information about the relationship between hypocalcemia risk and decreased kidney function, especially the higher risk of hypocalcemia in patients with severely decreased kidney function, was newly added to inform health care professionals of this risk [27–32].

Conclusion

The risk of hypocalcemia during BP prescription was found to be higher in patients with decreased kidney function, particularly those with severely decreased kidney function. The quantitative real-world evidence regarding the safety risk of BPs obtained in this study has led to the revision of the PI as a regulatory action in Japan and will contribute to promoting the proper use of BPs with appropriate risk management in clinical practice.

Abbreviations

aHR	Adjusted hazard ratio
Alb	Albumin
BP	Bisphosphonate preparation
Ca	Calcium
cHR	Crude hazard ratio
CI	Confidence interval
Cr	Creatinine
DPC	Diagnosis procedure combination
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
PI	Package insert
PMDA	Pharmaceuticals and Medical Devices Agency

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03553-7.

Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

All the authors designed the study. T.H., M.K., C.I., and K.K. performed the research and analyzed the data.T.H. and Y.U. were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset generated in the study is not publicly available due to the terms of use for MID-NET® to which we adhered when conducting this study; the accessibility of the dataset used for this analysis is restricted to specific authors including the corresponding author in a predetermined secure environment. No outside researchers are allowed to access the dataset.

Declarations

Ethics approval and consent to participate

As this study was conducted as an official activity of the PMDA under the Pharmaceuticals and Medical Devices Agency Law (Articles 15–5–(c) and (f)), it was not subject to a review through an institutional review board [33, 34] and the requirement for informed consent was waived. However, the opportunity of a patient to opt out from the MID-NET® was ensured by all MID-NET® cooperative hospitals.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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