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ORIGINAL ARTICLE

Frequency and determinants of serum calcium monitoring during eldecalcitol therapy in patients with osteoporosis

Kairi Ri[1] · Toshiki Fukasawa[1,2] · Soichiro Masuda[1,3] · Shiro Tanaka[4] · Masato Takeuchi[1] · Satomi Yoshida[1] · Koji Kawakami[1]

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Abstract

Introduction Eldecalcitol (ELD) is an active vitamin D_3 analog (AVD) commonly used to treat osteoporosis in Japan. Although routine monitoring of serum calcium levels during ELD therapy is recommended, little is known about the actual frequency and determinants of monitoring.

Materials and methods This was a descriptive cohort study using a Japanese electronic medical records database. We identified osteoporosis patients who initiated treatment with ELD or other AVDs (alfacalcidol and calcitriol) between April 1, 2011 and September 10, 2021. The index date for cohort entry was the first prescription date of ELD or other AVDs. The frequency of serum calcium monitoring was evaluated every 6 months. Determinants of serum calcium monitoring were identified using multivariable logistic regression models. We also calculated the incidence of hypercalcemia and the frequency of serum calcium monitoring within 6 months before hypercalcemia.

Results We identified 12,671 ELD users and 7867 other AVD users. Within 6 months after cohort entry, 45.9% of ELD users and 58.7% of other AVD users underwent serum calcium monitoring. Female sex, no use of systemic corticosteroids, moderate-to-good renal function, treatment in smaller hospitals, and treatment in orthopedic surgery departments were associated with a lower likelihood of receiving serum calcium monitoring during ELD therapy. The incidence of hypercalcemia among ELD users was 6.36 per 100 person-years, with 20.6% of cases not receiving serum calcium monitoring before hypercalcemia.

Conclusion Our findings suggest that serum calcium monitoring is not given adequate attention during ELD therapy in routine clinical practice.

Keywords Eldecalcitol · Hypercalcemia · Monitoring · Osteoporosis · Vitamin D

Introduction

Eldecalcitol (ELD), an active vitamin D_3 analog (AVD) approved in Japan and China, is a commonly used medication class for the treatment of osteoporosis, possibly due to its tolerability [1, 2]. The effect of ELD on bone mineral density is thought to be due to its strong inhibitory effect on bone resorption, in addition to the effect of conventional AVDs in promoting calcium absorption from the gastrointestinal tract [3]. Clinical trials have shown that ELD is more effective than alfacalcidol, a conventional AVD, in increasing bone mineral density and reducing the risk of vertebral and wrist fractures [4, 5].

A common side effect of ELD therapy is hypercalcemia, which can increase the risk of neurological symptoms, gastrointestinal symptoms, and renal disorders [6, 7].

✉ Satomi Yoshida
yoshida.satomi.4r@kyoto-u.ac.jp

1 Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan

2 Department of Digital Health and Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-Cho, Sakyo-Ku, Kyoto 606-8501, Japan

3 Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

4 Department of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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In a post-marketing observational study, the incidence of hypercalcemia during ELD therapy was 8.47% and 0.74% in patients with and without renal impairment, respectively [8]. A previous cohort study using a hospital administrative database which investigated the long-term safety of ELD in Japan documented that the incidence of hypercalcemia ranged from 0.23 to 0.94 per 100 person-years [9]. In Japan, it is recommended that serum calcium levels be monitored every 3 to 6 months during ELD therapy [10]. However, the Japanese regulatory authorities have reported some cases of ELD users who developed hypercalcemia, probably due to a lack of routine monitoring [10].

To our knowledge, the frequency of serum calcium monitoring during ELD therapy has yet to be studied. Additionally, the factors that influence serum calcium monitoring remain unidentified. This study aimed to investigate the frequency and determinants of serum calcium monitoring during ELD therapy in a real-world setting.

Materials and methods

Data source

We used longitudinal electronic medical records (EMR) data from the RWD database, which is managed by the Health, Clinic, and Education Information Evaluation Institute (HCEI, Kyoto, Japan) with assistance from Real World Data Co., Ltd. (Kyoto, Japan). As of 2022, the RWD database contained EMR data for approximately 23 million patients treated at over 220 clinics and hospitals in Japan [11]. The database contains information on demographics, inpatient and outpatient diagnoses, medical procedures, physician medication orders, and laboratory values, but does not contain hospital identifiers. Patient-level data can be tracked using unique, individual-level identifiers in the same medical institution. More details can be found in our previous works [12–14].

Study population

Using the database, we identified a cohort of osteoporosis patients aged ≥ 40 years who initiated treatment with ELD or other AVDs (alfacalcidol or calcitriol) between April 1, 2011 and September 10, 2021 (Supplementary Material 1). Other AVD users were used as comparators to understand in detail the characteristics of serum calcium monitoring in ELD users. The index date for cohort entry was defined as the first prescription date of ELD or other AVDs. All patients were required to have ≥ 1 year of continuous enrollment in the database before cohort entry. We included patients who continued AVD treatment for ≥ 6 months after cohort entry, because this study focused on describing the frequency of serum calcium monitoring among chronic AVD users. We excluded patients with a history of any of the following conditions sometimes misdiagnosed as osteoporosis: secondary malignant neoplasm of bone and bone marrow, osteomalacia, multiple myeloma and malignant plasma cell neoplasms, ankylosing spondylitis, Paget's disease of bone, or other disorders of bone density and structure (Supplementary Material S1).

Patients were followed from cohort entry until the end of the 3-year follow-up period, treatment discontinuation, treatment switch between ELD and other AVDs, death, or end of the study period (September 10, 2021), whichever occurred first. Treatment discontinuation was defined as no subsequent prescription during a 30-day grace period after the end of supply for the previous prescription.

Statistical analysis

Baseline characteristics are defined in Supplementary Material S2 and summarized by frequency and percentage [9, 15, 16]. Covariate imbalance at baseline between the ELD and other AVD groups was examined using standardized mean differences (SMDs), with values > 0.1 considered significantly different [17].

The frequency of serum calcium monitoring was evaluated every 6 months during the follow-up period. Mosaic plots were used to show the proportion of serum calcium monitoring during follow-up based on the history of monitoring before cohort entry. This was because serum calcium monitoring before cohort entry may imply routine monitoring for comorbidities. In a sensitivity analysis, the frequency of monitoring was evaluated every 3 months instead of every 6 months. Additionally, subgroup analyses were performed based on 1) individual factors, including age (40–59, 60–69, 70–79, ≥ 80 years), sex (male, female), concomitant osteoporosis medications (with, without), concomitant systemic corticosteroids (with, without), history of fracture (with, without), serum calcium monitoring before cohort entry (with, without), and estimated glomerular filtration rate (eGFR) (< 30, 30–60, ≥ 60 mL/min/1.73 m^2); and 2) institutional factors, including hospital size (< 100, 100–299, 300–499, ≥ 500 beds) and department (orthopedic surgery, internal medicine, others). Missing data on eGFR were addressed using multiple imputation by chained equations [18], with 20 imputed datasets created. The imputation models included all variables used for subgroup stratification and outcomes. Analyses were performed on each dataset and final estimates were obtained by combining the results across the datasets using Rubin's rule [19].

We conducted two additional analyses. First, we performed univariable and multivariable logistic regression to assess the association of individual and institutional factors with serum calcium monitoring. The multivariable

regression models included individual and institutional factors used for subgroup stratification. Second, we calculated the incidence of first hypercalcemia and the frequency of serum calcium monitoring within 6 months preceding hypercalcemia. We defined hypercalcemia as a total serum calcium levels of ≥ 11.0 mg/dL [9]. Because total serum calcium levels might not accurately reflect ionized calcium levels, we assessed two different serum calcium levels with and without serum albumin correction (Supplementary Material S2) [20]. In this analysis, unlike the primary analysis, patients who discontinued AVD treatment within 6 months after cohort entry were also included. This was because early discontinuation (within 6 months) of AVD treatment may often be associated with the occurrence of hypercalcemia, which could affect the estimates.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Ethics

This study was approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (No. R3089). Individual informed consent was not required due to the anonymous nature of the data. Consent for participation and publication was obtained by an opt-out approach from each medical institution.

Results

Baseline characteristics

We identified 109,153 patients who initiated ELD or other AVDs between April 2011 and September 2021 (Fig. 1). Of those, 12,671 ELD users and 7867 other AVD users met the eligibility criteria. Mean age was 74.1 years (SD, 9.2) in ELD users and 73.7 years (SD, 10.2) in other AVD users (Table 1). The proportion of females was 84.7% in ELD users, which was higher than the 74.8% observed in other AVD users. Mean values of laboratory tests among ELD users were as follows: corrected serum calcium 9.5 mg/dL (SD, 0.7), serum albumin 3.9 g/dL (SD, 0.5), eGFR 69.2 mL/min/1.73 m^2 (SD, 20.7), and HbA1c 6.2% (SD, 0.9). ELD users had higher mean values of corrected serum calcium, serum albumin, and eGFR compared to other AVD users. Of note, 44.6% of ELD users and 35.8% of other AVD users did not have serum calcium monitoring before cohort entry. The most common department was orthopedic surgery (56.1% in ELD users, 27.8% in other AVD users), followed by internal medicine (9.0% in ELD users, 16.4% in other AVD users).

Frequency of serum calcium monitoring

During the first 6 months after cohort entry, 45.9% (5817 of 12,671) of ELD users and 58.7% (4617 of 7867) of other AVD users underwent serum calcium monitoring (Fig. 2). Among them, 22.0% (1282 of 5817) of ELD users and 16.0% (737 of 4617) of other AVD users had not undergone serum calcium monitoring within 6 months before cohort entry. This pattern was consistent at every subsequent 6-month interval.

Similar results were obtained in a sensitivity analysis which analyzed monitoring frequency every 3 months (Supplemental Material S3): ELD users had a lower frequency of serum calcium monitoring than other AVD users.

Compared with the monitoring frequency in all ELD users (45.9%), frequency was lower for patients with the following factors (Table 2): age 60–79 years (43.9–45.4%), female (44.0%), concomitant use of osteoporosis medications (43.8%), no use of systemic corticosteroids (42.7%), absence of serum calcium monitoring before cohort entry (22.7%), eGFR ≥ 60 mL/min/1.73 m^2 (43.1%), hospitals with < 500 beds (36.9–45.2%), and orthopedic surgery department (40.2%).

Factors associated with receiving serum calcium monitoring

Multivariable logistic regression showed that the following factors were associated with a higher likelihood of receiving serum calcium monitoring in ELD users (Table 3): male sex (adjusted odds ratio [aOR], 1.23; 95% confidence interval [CI] 1.11–1.38), concomitant systemic corticosteroids (aOR, 1.77; 95% CI 1.56–2.00), history of serum calcium monitoring before cohort entry (aOR, 5.81; 95% CI 5.35–6.32), eGFR < 30 mL/min/1.73 m^2 (compared to ≥ 60 mL/min/1.73 m^2, aOR, 1.47; 95% CI 1.11–1.95), and treatment in an internal medicine department (compared to an orthopedic surgery department, aOR, 2.11; 95% CI 1.82–2.45). Conversely, age 60–69 years (compared to age ≥ 80 years, aOR, 0.87; 95% CI 0.78–0.98) and treatment in a smaller hospital (e.g. < 100 beds compared to ≥ 500 beds, aOR, 0.61; 95% CI 0.51–0.74) were associated with a lower likelihood of receiving monitoring.

Some differences in results were found in other AVD users: age (e.g., age 40–59 years compared to ≥ 80 years, aOR, 1.27; 95% CI 1.03–1.57), concomitant use of osteoporosis medications (aOR, 1.24; 95% CI 1.11–1.40), and eGFR 30–60 mL/min/1.73 m^2 (compared to ≥ 60 mL/min/1.73 m^2, aOR, 1.24; 95% CI 1.08–1.41) were associated with a higher likelihood of receiving serum calcium monitoring.

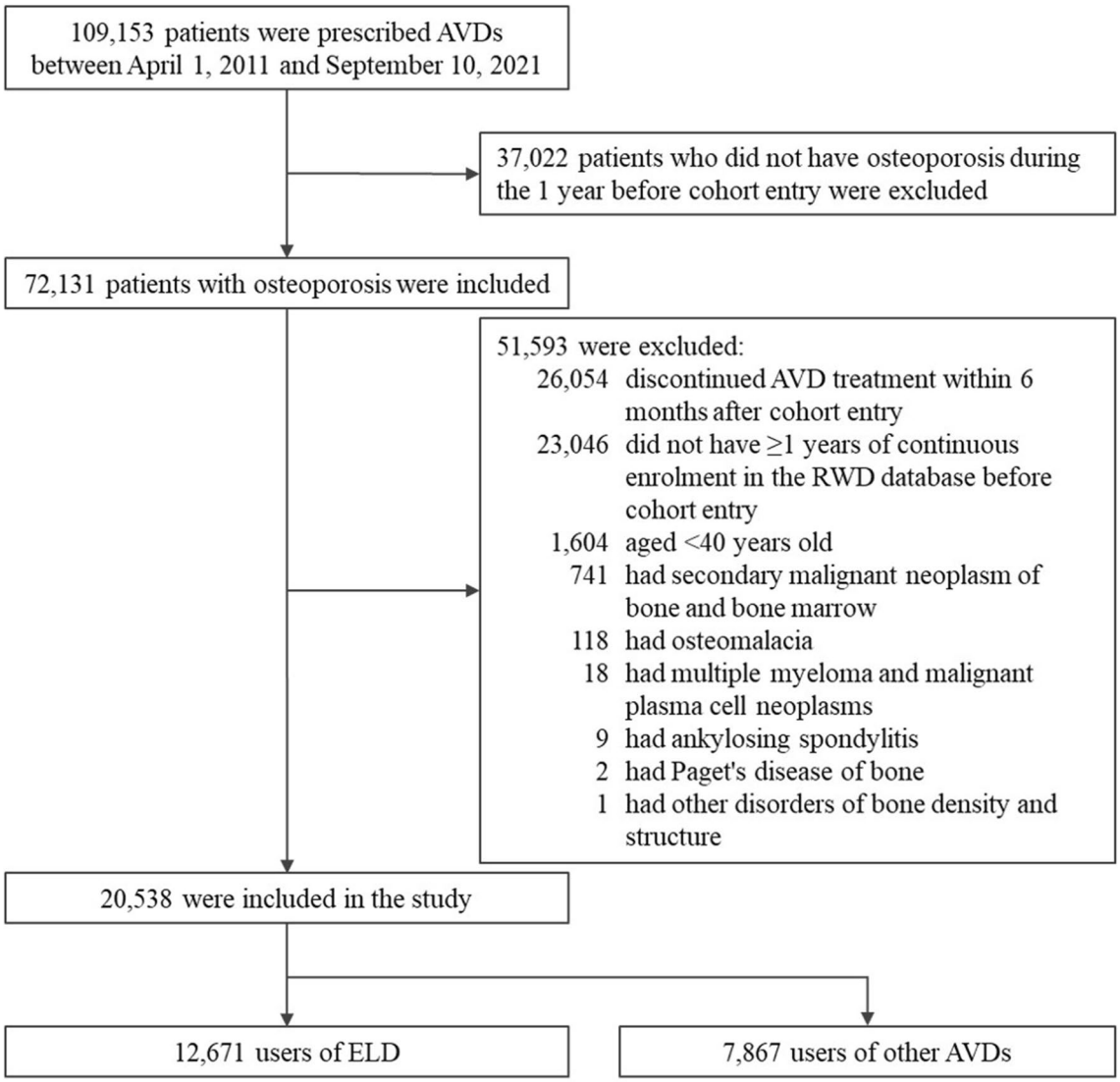

Fig. 1 Flow diagram of cohort selection, *AVD* Active vitamin D3 analog, *ELD* eldecalcitol, *ICD-10* International Classification of Diseases, Tenth Revision

Incidence of hypercalcemia and frequency of serum calcium monitoring before hypercalcemia

A total of 26,439 ELD users and 20,243 other AVD users were included in this additional analysis (Table 4). The incidence of first hypercalcemia, defined as an albumin-corrected serum calcium level of ≥11.0 mg/dL, was 6.36 (95% CI 6.03–6.68) and 7.99 (95% CI 7.53–8.44) per 100 person-years in the ELD and other AVD users, respectively. Of 1459 hypercalcemia cases in ELD users, 301 (20.6%) had not undergone monitoring within 6 months before hypercalcemia, while in other AVD users, 139 of 1167 cases (11.9%) had not undergone monitoring.

When hypercalcemia was redefined by uncorrected serum calcium levels, the incidence was 1.44 (95% CI 1.29–1.59) and 1.64 (95% CI 1.44–1.84) per 100 person-years in ELD and other AVD users, respectively. Of 348 hypercalcemia cases in ELD users, 77 (22.1%) had not undergone monitoring before the event, while in other AVD users, 28 of 255 cases (11.0%) had not undergone monitoring.

Discussion

This study is to our knowledge the first descriptive study of the frequency and determinants of serum calcium monitoring during ELD therapy in a real-world setting. The primary analysis revealed that only less than half of ELD users received serum calcium monitoring during treatment, despite the recommendation do so to minimize the risk

Table 1 Baseline characteristics of patients in the primary analysis

Characteristic	ELD users ($n=12,671$)		Other AVD users ($n=7867$)		SMD
Age (years), mean (SD)	74.1	(9.2)	73.7	(10.2)	0.034
40–59 years, *n* (%)	986	(7.8)	799	(10.2)	
60–69 years, *n* (%)	2556	(20.2)	1499	(19.1)	
70–79 years, *n* (%)	4907	(38.7)	2698	(34.3)	
≥ 80 years, *n* (%)	4222	(33.3)	2871	(36.5)	
Female sex, *n* (%)	10,730	(84.7)	5882	(74.8)	0.248
Year of cohort entry, *n* (%)					0.317
2011–2014	3060	(24.2)	3002	(38.2)	
2015–2018	6353	(50.1)	3509	(44.6)	
2019–2021	3258	(25.7)	1356	(17.2)	
Comorbidity, *n* (%)					
History of fracture	5572	(44.0)	2478	(31.5)	0.260
Malignancy	3726	(29.4)	2995	(38.1)	0.184
Hyperthyroidism	484	(3.8)	368	(4.7)	0.043
Hyperparathyroidism	178	(1.4)	325	(4.1)	0.167
Dementia	249	(2.0)	228	(2.9)	0.061
Parkinson's disease	256	(2.0)	209	(2.7)	0.042
Diabetes	3985	(31.5)	3128	(39.8)	0.174
COPD	3085	(24.4)	2074	(26.4)	0.046
Rheumatoid arthritis	1590	(12.6)	1238	(15.7)	0.092
Medication, *n* (%)					
Bisphosphonates	4573	(36.1)	2236	(28.4)	0.165
Calcitonin	260	(2.1)	73	(0.9)	0.093
SERM	1198	(9.5)	376	(4.8)	0.183
Teriparatide	614	(4.9)	274	(3.5)	0.068
Calcium	534	(4.2)	745	(9.5)	0.209
Denosumab	526	(4.2)	352	(4.5)	0.016
Vitamin K	215	(1.7)	221	(2.8)	0.075
Hormone replacement therapy	70	(1.0)	27	(0.3)	0.031
Systemic corticosteroids	1688	(13.3)	1885	(24.0)	0.386
Corrected serum calcium (mg/dL), mean (SD)	9.5	(0.7)	9.3	(0.8)	0.323
< 11.0 mg/dL, *n* (%)	6880	(54.3)	4942	(62.8)	
≥ 11.0 mg/dL, *n* (%)	138	(1.1)	112	(1.4)	
Missing, *n* (%)	5653	(44.6)	2813	(35.8)	
Serum albumin (g/dL), mean (SD)	3.9	(0.5)	3.8	(0.6)	0.261
< 4.0 g/dL, *n* (%)	4149	(32.7)	3676	(46.7)	
> 4.0 g/dL, *n* (%)	3599	(28.4)	2105	(26.8)	
Missing, *n* (%)	4923	(38.9)	2086	(26.5)	
eGFR (mL/min/1.73 m^2), mean (SD)	69.2	(20.7)	62.9	(27.6)	0.256
< 30 mL/min/1.73 m^2, *n* (%)	240	(1.9)	839	(10.7)	
30–60 mL/min/1.73 m^2, *n* (%)	2640	(20.8)	1827	(23.2)	
≥ 60 mL/min/1.73 m^2, *n* (%)	6346	(50.1)	3867	(49.2)	
Missing, *n* (%)	3445	(27.2)	1334	(17.0)	
HbA1c (%), mean (SD)	6.2	(0.9)	6.2	(1.0)	0.017
≤ 6.5%, *n* (%)	3415	(27.0)	2672	(34.0)	
> 6.5%, *n* (%)	1075	(8.5)	842	(10.7)	
Missing, *n* (%)	8181	(64.6)	4353	(55.3)	
Hospital size by number of beds, *n* (%)					0.205
< 100 beds	731	(5.8)	408	(5.2)	
100–299 beds	4753	(37.5)	2290	(29.1)	

Table 1 (continued)

Characteristic	ELD users ($n=12,671$)		Other AVD users ($n=7867$)		SMD
300–499 beds	4607	(36.4)	2923	(37.2)	
≥ 500 beds	2580	(20.4)	2246	(28.6)	
Department, *n* (%)					0.546
Orthopedic surgery	7112	(56.1)	2187	(27.8)	
Internal medicine	1136	(9.0)	1293	(16.4)	
Others	4423	(34.9)	4387	(55.8)	

AVD active vitamin D_3 analog, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *ELD* eldecalcitol; *HbA1c* hemoglobin A1c, *SD* standard deviation, *SERM* selective estrogen receptor modulator, *SMD* standardized mean difference

of hypercalcemia. Frequency among ELD users was less than that in other AVD users. A lower likelihood of receiving monitoring during ELD treatment was associated with female sex, no use of systemic corticosteroids, moderate-to-good renal function, treatment in a smaller hospital, and treatment in an orthopedic surgery department. The findings also indicated that ELD users were less likely to undergo serum calcium monitoring 6 months prior to developing hypercalcemia than other AVD users.

The importance of routine monitoring of serum calcium levels in patients treated with AVDs has been well documented [21, 22]. Consistent with a previous warning by Japanese regulatory authorities [10], our study confirmed that the current monitoring practices often do not adhere to these monitoring guidelines. More than half of ELD users did not receive routine serum calcium monitoring, with monitoring frequency being lower than that in other AVD users. Additionally, approximately 70–80% of ELD users with routine monitoring during the follow-up period had already received monitoring prior to cohort entry. These results suggest that sufficient attention is not paid to serum calcium monitoring at the initiation of ELD therapy. Of note, however, that the proportion of patients who did not receive monitoring prior to cohort entry but did receive it after cohort entry was higher in ELD users (22.0%) than in other AVD users (16.0%). This finding suggests that physicians may be more aware of the importance of routine monitoring during ELD treatment than during other AVD treatment.

With regard to the determinants of serum calcium monitoring during ELD therapy, we found that male sex, concomitant systemic corticosteroids, reduced renal function (eGFR < 30 mL/min/1.73 m^2), larger hospitals, and internal medicine departments were associated with a higher likelihood of monitoring. A previous study suggested that females are more likely to self-discontinue anti-osteoporosis medications than males [23]. We therefore speculate that women may have had lower adherence to scheduled medical visits for osteoporosis and relatively less monitoring than men. It is reasonable that corticosteroid use was associated with a higher likelihood of receiving serum calcium monitoring because it affects bone and calcium metabolism [24]. Regarding renal function, it is not surprising that a more severe disease prompts more frequent monitoring. Interestingly, AVD users—even those with an eGFR between 30 and 60 mL/min/1.73 m^2—underwent serum calcium monitoring more frequently than those with an eGFR ≥ 60 mL/min/1.73 m^2, whereas the frequency of monitoring among ELD users was not significantly different across the two eGFR groups. Given that hypercalcemia is a well-known risk factor for AKI with AVDs [6, 21], more attention should be paid to routine monitoring during ELD treatment to prevent AKI, even for those with mild renal impairment. It is possible that larger hospitals and internal medicine departments would demonstrate a higher likelihood of monitoring, as physicians affiliated with them are likely to be more aware of hypercalcemia risks.

Our calculated incidences of hypercalcemia per 100 person-years were higher than those reported in a previous Japanese study using real-world data, whether serum albumin levels were corrected or not (incidence of hypercalcemia without serum albumin correction in the previous study: ELD group, 0.23; other AVD group, 0.25) [9]. The incidence of hypercalcemia may have been underestimated in the previous study given that serum calcium levels were less likely to have been measured in that study than in the present study; the proportion of ELD users without baseline measurement was 57.9% in the previous study and 44.6% in this study [9]. In addition, our results using an EMR database from more than 200 clinics and hospitals are likely to be more generalizable than those of the previous study, which was based on laboratory data from only 39 of 415 acute care hospitals in the database [9, 11]. Among ELD users, 20.6–22.1% of hypercalcemia cases had not undergone monitoring before hypercalcemia, which was higher than that reported by Japanese regulatory authorities (1.0–3.8%) [10]. Of note, monitoring before hypercalcemia was less frequent in ELD users than in other AVD users. These findings suggest that some cases of hypercalcemia could have been more effectively managed by routine monitoring, particularly among ELD users, given that serum calcium monitoring plays an

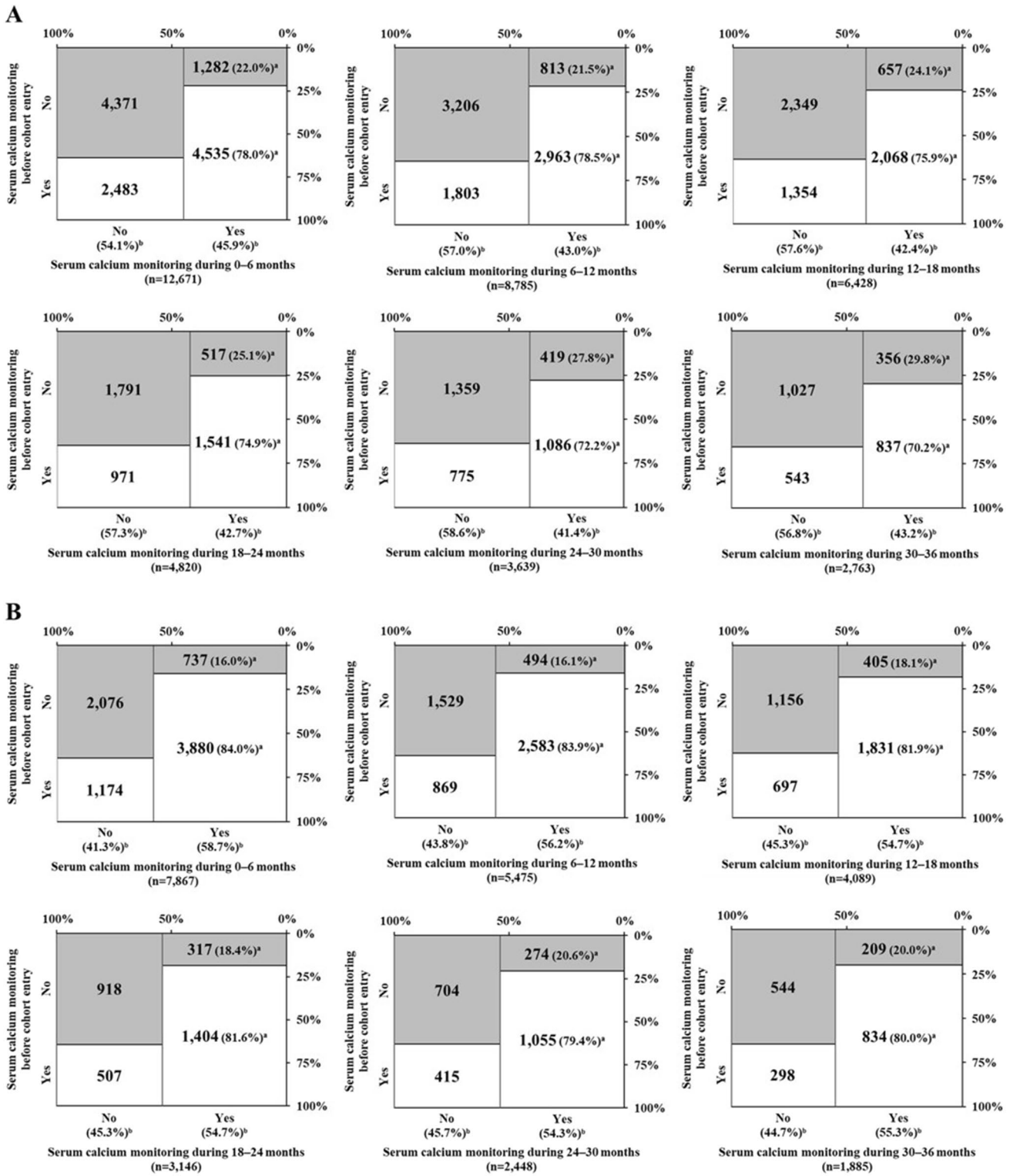

Fig. 2 Proportion of patients who underwent serum calcium monitoring after cohort entry among eldecalcitol users (**A**) and other active vitamin D_3 users (**B**), **a** proportion of serum calcium monitoring before cohort entry among patients who underwent serum calcium monitoring during each time period, and **b** frequency of serum calcium monitoring after cohort entry in all patients

Table 2 Proportion of patients who underwent serum calcium monitoring within 6 months after cohort entry in subgroups

Characteristic	ELD users ($n=12,671$)			Other AVD users ($n=7867$)		
	n	(%)	OR (95% CI)	*n*	(%)	OR (95% CI)
All patients	5817/12,671	(45.9)		4617/7867	(58.7)	
Age group						
40–59 years	499/986	(50.6)	1.17 (1.02–1.35)	552/799	(69.1)	1.86 (1.57–2.20)
60–69 years	1122/2556	(43.9)	0.90 (0.81–0.99)	894/1499	(59.6)	1.23 (1.08–1.39)
70–79 years	2227/4907	(45.4)	0.95 (0.88–1.03)	1603/2698	(59.4)	1.22 (1.09–1.35)
≥ 80 years	1969/4222	(46.6)	Reference	1568/2871	(54.6)	Reference
Sex						
Male	1094/1941	(56.4)	1.64 (1.49–1.81)	1453/1985	(73.2)	2.35 (2.10–2.62)
Female	4723/10,730	(44.0)	Reference	3164/5882	(53.8)	Reference
Concomitant osteoporosis medications						
Yes	3064/6991	(43.8)	0.83 (0.77–0.89)	2113/3692	(57.2)	0.89 (0.82–0.98)
No	2753/5680	(48.5)	Reference	2504/4175	(60.0)	Reference
Concomitant systemic corticosteroids						
Yes	1130/1688	(66.9)	2.72 (2.44–3.03)	1321/1885	(70.1)	1.91 (1.71–2.13)
No	4687/10,983	(42.7)	Reference	3296/5982	(55.1)	Reference
History of fracture						
Yes	2529/5572	(45.4)	0.96 (0.90–1.03)	1388/2478	(56.0)	0.85 (0.77–0.94)
No	3288/7099	(46.3)	Reference	3229/5389	(59.9)	Reference
Serum calcium monitoring before cohort entry						
Yes	4535/7018	(64.6)	6.23 (5.75–6.74)	3880/5054	(76.8)	9.31 (8.37–10.4)
No	1282/5653	(22.7)	Reference	737/2813	(26.2)	Reference
eGFR						
< 30 mL/min/1.73 m^2	159/241	(66.0)	1.51 (1.18–1.94)	798/853	(93.6)	7.24 (5.72–9.17)
30–60 mL/min/1.73 m^2	1515/2822	(53.7)	1.09 (0.99–1.19)	1249/2056	(60.8)	1.15 (1.03–1.29)
≥ 60 mL/min/1.73 m^2	4143/9608	(43.1)	Reference	2570/4958	(51.8)	Reference
Hospital size by number of beds						
< 100 beds	270/731	(36.9)	0.37 (0.32–0.44)	225/408	(55.2)	0.34 (0.27–0.42)
100–299 beds	1891/4753	(39.8)	0.42 (0.38–0.46)	1076/2290	(47.0)	0.37 (0.33–0.42)
300–499 beds	2080/4607	(45.2)	0.52 (0.48–0.58)	1771/2923	(60.6)	0.64 (0.57–0.72)
≥ 500 beds	1576/2580	(61.1)	Reference	1587/2246	(70.7)	Reference
Department						
Orthopedic surgery	2862/7112	(40.2)	Reference	962/2187	(44.0)	Reference
Internal medicine	682/1136	(60.0)	2.23 (1.96–2.54)	816/1293	(63.1)	2.18 (1.89–2.51)
Others	2273/4423	(51.4)	1.57 (1.46–1.69)	2839/4387	(64.7)	2.34 (2.10–2.59)

AVD active vitamin D_3 analog, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *ELD* eldecalcitol, *OR* odds ratio

important role in the early detection of hypercalcemia, which is often asymptomatic [7]. Future interventions aimed at improving adherence to monitoring guidelines are needed for the safe use of ELD, together with identifying factors which influence the occurrence of hypercalcemia other than monitoring practices, such as renal impairment [7].

This study has several limitations. First, no information about the purpose of serum calcium monitoring was available in our database and some of the monitoring observed may have been included in routine laboratory testing for comorbidities rather than for specific monitoring the management of hypercalcemia induced by ELD. To describe the frequency of monitoring specifically for ELD therapy, we evaluated the frequency of serum calcium monitoring stratified by whether it had ever been performed before cohort entry. Second, the generalizability of the results is limited, because the RWD database does not evenly cover medical institutions across Japan and may not be fully representative. In this study, only a small percentage of ELD and other AVD users received treatment at clinics or small hospitals (fewer than 100 beds).

Table 3 Multivariable logistic regression analyses of the association between patient characteristics and presence of serum calcium monitoring within 6 months after cohort entry

Characteristic	aOR (95% CI)[a]	
	ELD users ($n=12,671$)	Other AVD users ($n=7867$)
Age		
40–59 years	0.90 (0.77–1.06)	1.27 (1.03–1.57)
60–69 years	0.87 (0.78–0.98)	1.03 (0.88–1.21)
70–79 years	0.95 (0.86–1.04)	1.12 (0.99–1.28)
≥ 80 years	Reference	Reference
Sex		
Male	1.23 (1.11–1.38)	1.54 (1.35–1.77)
Female	Reference	Reference
Concomitant osteoporosis medications		
Yes	0.96 (0.88–1.04)	1.24 (1.11–1.40)
No	Reference	Reference
Concomitant systemic corticosteroids		
Yes	1.77 (1.56–2.00)	1.19 (1.03–1.36)
No	Reference	Reference
History of fracture		
Yes	0.93 (0.85–1.01)	1.00 (0.88–1.13)
No	Reference	Reference
Serum calcium monitoring before cohort entry		
Yes	5.81 (5.35–6.32)	7.74 (6.91–8.66)
No	Reference	Reference
eGFR		
< 30 mL/min/1.73 m^2	1.47 (1.11–1.95)	5.09 (3.91–6.63)
30–60 mL/min/1.73 m^2	1.08 (0.98–1.20)	1.24 (1.08–1.41)
≥ 60 mL/min/1.73 m^2	Reference	Reference
Hospital size by number of beds		
< 100 beds	0.61 (0.51–0.74)	0.48 (0.37–0.63)
100–299 beds	0.66 (0.59–0.74)	0.49 (0.42–0.57)
300–499 beds	0.66 (0.59–0.73)	0.68 (0.59–0.78)
≥ 500 beds	Reference	Reference
Department		
Orthopedic surgery	Reference	Reference
Internal medicine	2.11 (1.82–2.45)	2.20 (1.84–2.63)
Others	1.41 (1.30–1.55)	1.80 (1.57–2.07)

aOR adjusted odds ratio, *AVD* active vitamin D_3 analog, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *ELD* eldecalcitol

[a]Adjusted for age, sex, hospital size by number of beds, department, concomitant osteoporosis medications, concomitant systemic corticosteroids, history of fracture, presence of serum calcium monitoring before cohort entry, and eGFR

In conclusion, our descriptive study suggests a lack of attention to monitoring serum calcium levels during ELD therapy in routine care. Our findings highlight the real-world practice of serum calcium monitoring in patients undergoing ELD therapy for osteoporosis, and will contribute to the optimization of monitoring strategies and informing of healthcare professionals on factors that influence adherence to monitoring guidelines.

Table 4 Incidence rate of hypercalcemia and proportion of patients who did not undergo serum calcium monitoring within 6 months before hypercalcemia

	No. of hypercalcemia cases	Incidence per 100 person-years (95% CI)	No. of the cases without serum calcium monitoring before hypercalcemia (%)[a]
Hypercalcemia, corrected by serum albumin level			
ELD users ($n=26,439$)	1459	6.36 (6.03–6.68)	301/1459 (20.6)
Other AVD users ($n=20,243$)	1167	7.99 (7.53–8.44)	139/1167 (11.9)
Hypercalcemia, uncorrected total serum calcium level			
ELD users ($n=26,439$)	348	1.44 (1.29–1.59)	77/348 (22.1)
Other AVD users ($n=20,243$)	255	1.64 (1.44–1.84)	28/255 (11.0)

AVD active vitamin D_3 analog, *CI* confidence interval, *ELD* eldecalcitol

[a]Serum calcium monitoring within 6 months before hypercalcemia was investigated. Hypercalcemia was defined as a serum calcium level of ≥ 11.0 mg/dL

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Author contributions All authors were involved in formulating the study concept and design. KR performed the statistical analysis. KR and TF wrote the manuscript. All authors contributed to the discussion and reviewed, edited, and approved the final manuscript as submitted.

Declarations

Conflict of interest Toshiki Fukasawa has been employed by the Department of Digital Health and Epidemiology, an Industry-Academia Collaboration Course supported by Eisai Co., Ltd., Kyowa Kirin Co., Ltd., and Real World Data Co., Ltd.; and has received consulting fees from Real World Data Co., Ltd. and speaker fees from Asahi Kasei Pharma Corporation and EPS Corporation. Shiro Tanaka has received lecture fees from Bayer Yakuhin, Amgen Astellas BioPharma K.K. and Research Institute of Healthcare Data Science; consulting fees from Boehringer Ingelheim; outsourcing fees from the Public Health Research Foundation; grants from Novo Nordisk Pharma Ltd., the Japan Agency for Medical Research and Development, the Japanese Ministry of Health Labor and Welfare, and the Japanese Ministry of Education, Science, and Technology. Masato Takeuchi has received consulting fees from Eisai Co., Ltd. Satomi Yoshida was employed by the Department of Digital Health and Epidemiology, an Industry-Academia Collaboration Course supported by Eisai Co., Ltd., Kyowa Kirin Co., Ltd., and Real World Data Co., Ltd.; and has received consulting fees from Real World Data Co., Ltd. Koji Kawakami has received research funds from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., OMRON Corporation, Toppan Inc., and Real World Data Co., Ltd.; consulting fees from Advanced Medical Care Inc., JMDC Inc., and Shin Nippon Biomedical Laboratories Ltd.; executive compensation from Cancer Intelligence Care Systems, Inc.; honoraria from Chugai Pharmaceutical Co., Ltd., and Pharma Business Academy; and has held stock in Real World Data Co., Ltd. All other authors declare no potential conflicts of interest.

References

1. Cui L, Xia W, Yu C, Dong S, Pei Y (2022) Overview of the clinical efficacy and safety of eldecalcitol for the treatment of osteoporosis. Arch Osteoporos 17:74
2. Fujiwara S, Miyauchi A, Hamaya E, Nicholls RJ, Weston A, Baidya S, Pinto L, Barron R, Takada J (2018) Treatment patterns in patients with osteoporosis at high risk of fracture in Japan: retrospective chart review. Arch Osteoporos 13:34
3. Noguchi Y, Kawate H, Nomura M, Takayanagi R (2013) Eldecalcitol for the treatment of osteoporosis. Clin Interv Aging 8:1313–1321
4. Matsumoto T, Ito M, Hayashi Y, Hirota T, Tanigawara Y, Sone T, Fukunaga M, Shiraki M, Nakamura T (2011) A new active vitamin D3 analog, eldecalcitol, prevents the risk of osteoporotic fractures–a randomized, active comparator, double-blind study. Bone 49:605–612
5. Xu Z, Fan C, Zhao X, Tao H (2016) Treatment of osteoporosis with eldecalcitol, a new vitamin D analog: a comprehensive review and meta-analysis of randomized clinical trials. Drug Des Devel Ther 10:509–517
6. Aihara S, Yamada S, Oka H, Kamimura T, Nakano T, Tsuruya K, Harada A (2019) Hypercalcemia and acute kidney injury induced by eldecalcitol in patients with osteoporosis: a case series of 32 patients at a single facility. Ren Fail 41:88–97
7. Walker MD, Shane E (2022) Hypercalcemia: a review. JAMA 328:1624–1636
8. Saito H, Kakihata H, Nishida Y, Yatomi S, Nihojima S, Kobayashi Y, Tabata H, Nomura M (2017) The safety and effectiveness profile of eldecalcitol in a prospective, post-marketing observational study in Japanese patients with osteoporosis: interim report. J Bone Miner Metab 35:456–463
9. Takeuchi Y, Saito H, Makishima M, Yokoyama H, Yamaguchi T, Fujii H, Inoue E, Isemura T, Kondo S, (2022) Long-term safety of eldecalcitol in Japanese patients with osteoporosis: a retrospective, large-scale database study. J Bone Miner Metab 275–291
10. Pharmaceuticals and Medical Devices Agency alert for proper use of drugs. Hypercalcemia induced by eldecalcitol and compliance with laboratory testing. Available: https://www.pmda.go.jp/files/000237333.pdf. Accessed Jan, 2023.

11. Pharmacoepidemiology & Database Taskforce, Japanese Society for Pharmacoepidemiology. Survey of Japanese databases in Japan available for clinical/pharmacoepidemiology. Available: http://www.jspe.jp/committee/020/0210/. Accessed Jan, 2023.
12. Ri K, Fukasawa T, Yoshida S, Takeuchi M, Kawakami K (2023) Risk of parkinsonism and related movement disorders with gabapentinoids or tramadol: A case-crossover study. Pharmacotherapy 43:136–144
13. Yoshida S, Takeuchi M, Tanaka-Mizuno S, Mizuno K, Nakashima M, Fukasawa T, Kawakami K (2022) Clinical epidemiology and pharmacoepidemiology studies with real-world databases. Proceedings of the Japan Academy, Series B 98:517–528
14. Hashimoto H, Takeuchi M, Kawakami K (2022) Association between biopsies for anti-neutrophil cytoplasmic antibody-associated vasculitis and prognosis: a retrospective cohort study. Clin Rheumatol 41:541–548
15. Usui T, Funagoshi M, Seto K, Ide K, Tanaka S, Kawakami K (2018) Persistence of and switches from teriparatide treatment among women and men with osteoporosis in the real world: a claims database analysis. Arch Osteoporos 13:54
16. Lyu H, Yoshida K, Zhao SS, Wei J, Zeng C, Tedeschi SK, Leder BZ, Lei G, Tang P, Solomon DH (2020) Delayed Denosumab injections and fracture risk among patients with osteoporosis. Ann Intern Med 173:516–526
17. Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083–3107
18. Mulla ZD, Seo B, Kalamegham R, Nuwayhid BS (2009) Multiple imputation for missing laboratory data: an example from infectious disease epidemiology. Ann Epidemiol 19:908–914
19. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338:b2393
20. National Kidney Foundation (2003) K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42:S1-201
21. Jean G, Souberbielle JC, Chazot C (2017) Vitamin D in chronic kidney disease and dialysis patients. Nutrients 9:328
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group (2017) KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 7:1–59
23. Deng Y-L, Hsu C-S, Hsu C-Y, Chen C-H, Ou S-F, Liu C-F, Yang S-H, Shih C-H, Chen Y-M, Lee H-T (2022) Predictors for self-discontinuation of anti-osteoporosis medication: a hospital-based real-world study. PLoS ONE 17:e0275020
24. Dennis MW (2018) Clinical pharmacology of corticosteroids. Respir Care 63:655