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Received: 1 February 2022 | Revised: 18 March 2022 | Accepted: 28 March 2022

DOI: 10.1002/ccr3.5713

CASE REPORT

Clinical Case Reports Open Access WILEY

Relationship between patients' characteristics and efficacy of calcimimetics for primary hyperparathyroidism in the elderly

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Funding information
None

Abstract

Calcimimetic treatment has been reported to be effective for primary hyperparathyroidism (PHPT). Nine elderly PHPT patients who had been treated with calcimimetics were retrospectively analyzed. It was found that calcimimetics can reduce elevated serum calcium levels in elderly PHPT patients with low femoral DEXA %YAM and low urinary cAMP levels.

KEYWORDS

cinacalcet, evocalcet, hypercalcemia, primary hyperparathyroidism

1 | INTRODUCTION

Primary hyperparathyroidism (PHPT) is the most common disorder causing hypercalcemia, which occurs mainly in elderly women.[1] Patients with PHPT present symptoms including nephrolithiasis, bone fracture, and cognitive impairment or can be asymptomatic.[1,2] Excessive secretion of parathyroid hormone (PTH) leads to elevated serum levels of calcium and alkaline phosphatase and decreased serum level of inorganic phosphate.[2] PHPT is most often caused by excessive secretion of PTH from a single adenoma (80%–85% of cases).[1]

Parathyroidectomy is the established treatment with a good prognosis for PHPT due to a single parathyroid adenoma,[3] and the treatment reduces elevated serum levels of calcium and PTH, increases bone mineral density (BMD),[4,5] reduces the occurrence of bone fractures,[6,7] and decreases the risk of renal stones.[8] However, some PHPT patients, especially elderly patients, refuse to undergo surgical therapy for various reasons including perceived risk.[1,9]

Treatment with calcimimetics, including cinacalcet and evocalcet, has also been reported to be effective for reducing elevated serum calcium level in PHPT patients[10,11]; however, the relationship between the efficacy of calcimimetics for PHPT and patient characteristics related to the effectiveness of calcimimetics remains unknown. To investigate the relevance of clinical parameters to the effectiveness of calcimimetics for PHPT, we retrospectively analyzed PHPT patients who were treated with calcimimetics in our department.

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2 | PATIENTS AND METHODS

2.1 | Study design

We conducted a single-center cross-sectional study. PHPT patients who had been treated with calcimimetics in our department between 2018 and 2020 were retrospectively reviewed. The present study was approved by the Ethical Committee of Okayama University Hospital (K2103-021) and adhered to the Declaration of Helsinki.

2.2 | Analysis of clinical parameters

Information on the patients' medical histories was obtained from hospital medical records. Information on age, gender, race, and body mass index (BMI) was also obtained. Information on the following biochemical parameters was also obtained: white blood cells, hemoglobin, and platelets for blood cell counts; alkaline phosphatase (ALP), calcium (Ca), corrected Ca (cCa), inorganic phosphate (iP), intact parathyroid hormone (PTH), whole PTH, fractional excretion of calcium (FECa), %tubular reabsorption of phosphate (%TRP), cyclic adenosine monophosphate (cAMP), urinary cAMP, nephrogenous cAMP, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), 25-hydroxyvitamin D (25(OH)D), and $1,25(OH)_2D/25(OH)D$ ratio for calcium metabolism; and albumin, total protein, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, chloride, magnesium, blood urea nitrogen, creatinine, thyroid-stimulating hormone, and free thyroxine for liver, renal, and thyroid functions. Serum Ca levels were corrected in patients with hypoalbuminemia according to the following formula: serum cCa level (mg/dL) = serum Ca level (mg/dL) + (4 - (serum albumin level) (g/dL)).[12] To calculate reduction rates of serum cCa levels, we used the following formula: reduction rate of serum cCa level (%) = (((serum cCa levels before calcimimetic treatment (mg/dL)) - (serum cCa levels after calcimimetic treatment (mg/dL)))/(serum cCa levels before calcimimetic treatment (mg/dL))) x100. The level of 25(OH)D was determined by a chemiluminescence immunoassay, the levels of $1,25(OH)_2D$ and cAMP were determined by a radioimmunoassay, and the level of intact PTH was determined by an immunoradiometric assay at LSI Medience Corporation (Tokyo). The level of whole PTH was determined by a chemiluminescent enzyme immunoassay at the Central Laboratory of Okayama University Hospital. An auto-analyzer system at the Central Laboratory of Okayama University Hospital was used for determining the levels of other parameters. Dual energy X-ray absorptiometry % young adult mean (DEXA %YAM) in the femoral neck and lumbar spine was measured as we previously reported.[13]

2.3 | Statistical analysis

For statistical analyses, we used EZR, version 1.40 (Saitama Medical Center, Jichi Medical University), which is a modified version from R commander (The R Foundation for Statistical Computing).[14] The Mann–Whitney *U* test and Spearman's rank correlation coefficient, which were treated as two-sided, we used for statistic continuous measurements. We regarded *p* values less than 0.05 as statistically significant.

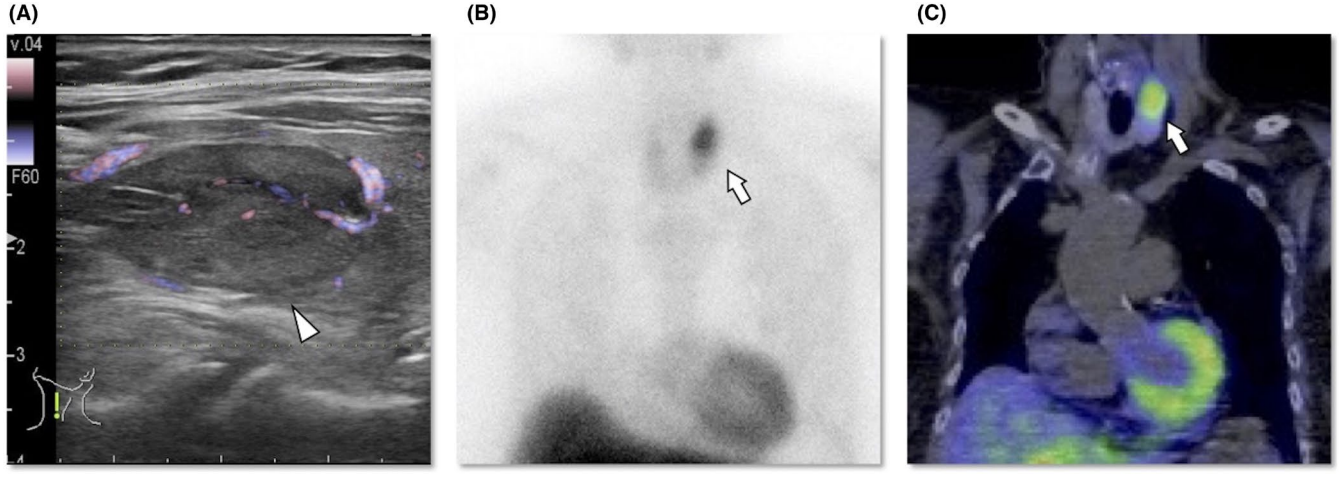

FIGURE 1 Representative radiologic findings of PHPT. Findings of cervical ultrasound with blood flow assessment (A, arrowhead), ^{99m}Tcsestamibi nuclear scintigraphy (B, arrow), and single photon emission computed tomography/computed tomography (C, arrow) are shown. PHPT: primary hyperparathyroidism

3 | RESULTS

3.1 | Patients' characteristics and BMD

Nine patients including 8 females (88.9%) and one male (11.1%), who were all Japanese, were included in this study. The etiology of PHPT was diagnosed as a parathyroid adenoma in 8 patients (88.9%) based on the findings of cervical ultrasound, computed tomography (CT), and ^{99m}Tcsestamibi nuclear scintigraphy. Representative radiologic findings in PHPT patients are shown in Figure 1. An 87-year-old female patient was diagnosed with PHPT due to an upper left parathyroid adenoma, which was shown in cervical ultrasound with blood flow assessment (Figure 1A), ^{99m}Tcsestamibi nuclear scintigraphy (Figure 1B), and single photon emission computed tomography/computed tomography (SPECT/CT) (Figure 1C). The other patient (11.1%) was diagnosed with PHPT, but localization of the parathyroid tumor was not detected by CT or SPECT/CT. For calcimimetic treatment, cinacalcet (25 mg) was used in 6 (66.7%) of the patients and evocalcet (1 mg) was used in 3 (33.3%) of the patients. The median age of the patients was 81 years (interquartile range (IQR): 61–86 years) and median BMI was 25.6 kg/m^2 (22.4–26.7 kg/m^2). Median DEXA %YAM of the PHPT patients was deteriorated to 63% (53%–74%) in the femoral neck, which was less than 70% as the definition of osteoporosis,[15] but was preserved in the lumbar spine (82% (78%–87%)). Medical histories of the patients included nephrolithiasis in one patient (11.1%), osteoporosis in 3 patients (33.3%), bone fracture in 3 patients (33.3%), hypertension in 7 patients (77.8%), and dementia in one patient (11.1%). None of the patients had a familial history suggesting familial hypocalciuric hypercalcemia or multiple endocrine neoplasia. Various drugs including thiazides, bisphosphonates, denosumab, and lithium can be associated with secondary hyperparathyroidism,[16] and two of the nine patients in the present study were taking bisphosphonates for osteoporosis. The clinical characteristics of the patients are summarized in Table 1.

TABLE 1 Clinical and biochemical characteristics of PHPT patients

Patients' characteristics	Number (%)
Gender	
Female	8 (88.9)
Male	1 (11.1)
Etiology of PHPT	
Parathyroid adenoma	8 (88.9)
Calcimimetic treatment	
Cinacalcet	6 (66.7)
Evocalcet	3 (33.3)
Medical history	
Nephrolithiasis	1 (11.1)
Osteoporosis	3 (33.3)
Bone fracture	3 (33.3)
Hypertension	7 (77.8)
Dementia	1 (11.1)
Clinical data	Median (Interquartile range)
Age (years)	81 (61–86)
BMI (kg/m^2)	25.6 (22.4–26.7)
DEXA %YAM (%)	
Femoral neck	63 (53–74)
Lumbar spine	82 (78–87)
Baseline laboratory data	Median (Interquartile range)
cCa (mg/dL)	11.1 (10.5–12.7)
iP (mg/dL)	2.3 (2.3–2.4)
Mg (mg/dL)	2.0 (1.9–2.0)
ALP (U/L)	114.5 (100.5–125)
1,25(OH)$_2$D (pg/mL)	80 (64–111)
1,25(OH)$_2$D/25(OH)D ratio	13.8×10^{-3} ($7.8–17.3 \times 10^{-3}$)
Intact PTH (pg/mL)	251.0 (198.3–498.5)
Whole PTH (pg/mL)	186.0 (165.7–443.9)
FECa (%)	1.3 (1.12–1.48)
%TRP (%)	79.9 (77.1–83.9)
Urinary cAMP (μmoL/day)	4.3 (4.0–5.3)
Nephrogenous cAMP (nmoL/dL GF)	3.4 (2.4–4.0)

Abbreviations: %TRP, %tubular reabsorption of phosphate; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; BMI, body mass index; cAMP, cyclic adenosine monophosphate; cCa, corrected calcium; DEXA %YAM, dual energy X-ray absorptiometry % young adult mean; FECa, fractional excretion of calcium; iP, inorganic phosphorus; Mg, magnesium; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

3.2 | Baseline laboratory data for PHPT patients

Laboratory tests before treatment showed a high median cCa serum level of 11.1 (IQR: 10.5–12.7) mg/dL, low iP serum level of 2.3 (2.3–2.4) mg/dL, normal magnesium serum level of 2.0 (1.9–2.0) mg/dL, and high ALP serum level of 114.5 (100.5–125) U/L. Serum level of 1,25(OH)$_2$D and 1,25(OH)$_2$D/25(OH)D ratio was high: 80 (64–111) pg/mL and 13.8×10^{-3} ($7.8–17.3 \times 10^{-3}$), respectively. Plasma levels of intact PTH and whole PTH were elevated: 251.0 (198.3–498.5) pg/mL and 186.0 (165.7–443.9) pg/mL, respectively. The fractional excretion of Ca was higher than 1% (1.3% (1.12%–1.48%)), %tubular reabsorption of

phosphate was low (79.9% (77.1%–83.9%)), urinary cAMP was normal (4.3 (4.0–5.3) μmoL/day), and nephrogenous cAMP was high (3.4 (2.4–4.0) nmoL/dL GF). The biochemical characteristics of the patients are summarized in Table 1.

3.3 | Effects of calcimimetics on biochemical parameters in PHPT patients

The median treatment duration was 22 days (IQR: 20–29 days) at the first visit follow-up after the start of calcimimetic treatment. Administration of calcimimetics reduced serum cCa levels (median, 10.5; IQR, 9.7–11.6) (Figure 2A), decreased serum iP levels (2.6; 2.2–2.8) (Figure 2B), and reduced PTH levels (intact PTH: 218; 141.0–389.5; whole PTH: 140.2; 96.8–223.6) (Figure 2C), though the differences were not statistically significant.

3.4 | Relevance of clinical parameters to calcimimetic treatment for PHPT patients

Since hypercalcemia is a biological hallmark of PHPT,[2] we evaluated reduction of serum cCa levels. The median reduction rate of serum cCa level was 5.8% (IQR: 0%–13.4%). It was notable that reduction rate of serum cCa level had significant correlations with age ($R = 0.95$, $p < 0.01$) (Figure 3A), DEXA %YAM in the femoral neck ($R = -0.92$, $p < 0.01$) (Figure 3B), and urinary cAMP level ($R = -0.85$, $p < 0.01$) (Figure 3C). Other clinical parameters including PTH, FECa, and %TRP did not correlate with reduction rate of serum cCa level, as shown in Table 2.

4 | DISCUSSION

To the best of our knowledge, this is the first study in which the relationship between clinical characteristics of

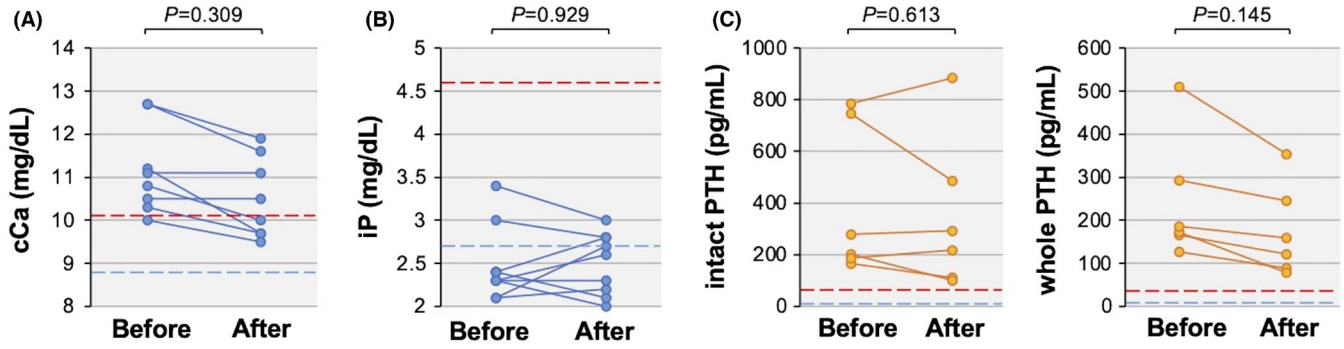

FIGURE 2 Changes in laboratory markers with calcimimetic treatment in PHPT patients. Serum levels of cCa (A), iP (B), and intact PTH and whole PTH (C) before and after treatment with calcimimetics are shown. cCa: corrected calcium; iP: inorganic phosphate; PTH: parathyroid hormone; and PHPT: primary hyperparathyroidism. Red dotted lines show upper limits of normal ranges, and blue dotted lines show lower limits of normal ranges

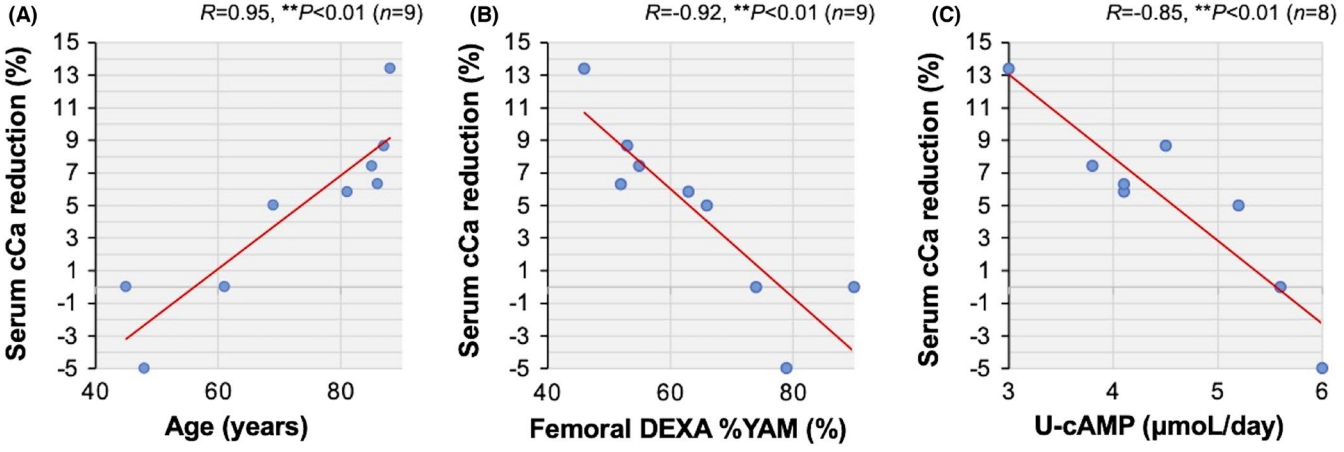

FIGURE 3 Correlations of reduction rate of serum corrected calcium levels with clinical parameters in PHPT patients treated with calcimimetics. Reduction rate of serum calcium levels had a significant positive correlation with age (A) and significant negative correlations with DEXA %YAM in the femoral neck (B) and urinary cAMP (C). DEXA %YAM: dual energy X-ray absorptiometry % young adult mean; and cAMP: cyclic adenosine monophosphate

TABLE 2 Correlations between reduction rate of serum cCa level and clinical parameters

Comparison	With reduction rate of serum cCa level		
	number	*R*	*p* values
Patients' profile			
Age	9	0.95	0.000066**
BMI	9	−0.084	0.83
Blood cell count			
White blood cell	9	−0.092	0.81
Hemoglobin	9	−0.35	0.35
Platelet	9	−0.059	0.88
Calcium metabolism			
Inorganic phosphate	9	0.42	0.27
ALP	9	0.13	0.75
Intact PTH	8	0.20	0.63
Whole PTH	9	−0.18	0.65
FECa	9	0.29	0.44
%TRP	9	0.49	0.19
cAMP	8	0.49	0.22
Urinary cAMP	8	−0.85	0.0075**
Nephrogenous cAMP	8	0.29	0.50
$1,25(OH)_2D$	9	0.23	0.56
25(OH)D	7	−0.63	0.13
$1,25(OH)_2D$/25(OH)D ratio	7	0.71	0.088
Liver, renal, and thyroid functions			
Total protein	9	−0.37	0.33
Albumin	9	−0.52	0.15
AST	9	0.35	0.36
ALT	9	−0.24	0.53
Sodium	9	0.33	0.39
Potassium	9	−0.33	0.39
Chloride	9	−0.19	0.62
Magnesium	8	0.28	0.51
BUN	9	0.025	0.95
Creatinine	9	−0.15	0.71
TSH	9	0.11	0.78
FT4	9	0.20	0.60
Bone mineral density			
DEXA %YAM (Femoral neck)	9	−0.92	0.00043**
DEXA %YAM (Lumbar spine)	9	−0.58	0.099

Abbreviations: %TRP, %tubular reabsorption of phosphate; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; cAMP, cyclic adenosine monophosphate; cCa, corrected calcium; DEXA %YAM, dual energy X-ray absorptiometry % young adult mean; FECa, fractional excretion of calcium; FT4, free thyroxine; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

** $p < 0.01$, statistically significant between the indicated factors.

PHPT patients treated with calcimimetics and the treatment effects was examined. The patients in the present study had typical characteristics of PHPT: hypercalcemia, hypophosphatemia, elevated serum levels of PTH and $1,25(OH)_2D$, and deterioration of DEXA% YAM in the femoral neck but not in the lumbar spine.[1,2] The results of

our study suggested that administration of calcimimetics for about three weeks reduces elevated serum levels of cCa and intact PTH in PHPT patients. Notably, the reduction rate of serum cCa levels by calcimimetic treatment had a significant positive correlation with age and significant negative correlations with DEXA %YAM in the femoral neck and urinary cAMP level.

PHPT affects postmenopausal women much more commonly than men.[2] Serum calcium level should be routinely measured for screening of PHPT, and asymptomatic PHPT patients have been increasingly diagnosed.[2] Localization of the parathyroid tumor is determined by cervical ultrasonography, ^{99m}Tcsestamibi nuclear scintigraphy, SPECT/CT, or contrast-enhanced CT.[2] Considering the possibility of ectopic PHPT, chest imaging tests of CT, and ^{99m}Tcsestamibi nuclear scintigraphy should be included.[17]

Parathyroidectomy is always a treatment option for PHPT patients in whom parathyroid lesions were detected, since surgery is the only definitive therapy.[18] A surgical approach is recommended for both asymptomatic patients and symptomatic patients with PHPT if they meet the following criteria: (1): serum calcium level of 1.0 mg/dL more than the upper limit of the normal range, (2) T-score of BMD determined by DEXA of less than −2.5 at the lumbar spine, total hip, femoral neck, or distal 1/3 radius or vertebral fracture detected by X-ray, CT, magnetic resonance imaging, or vertebral fracture assessment, (3) creatinine clearance of less than 60 mL/min, 24 h urine for calcium of more than 400 mg/day, increased stone risk determined by biochemical stone risk analysis, or presence of nephrolithiasis or nephrocalcinosis detected by X-ray, ultrasound, or CT, or (4) age of less than 50 years.[18] However, some PHPT patients are medically unfit for parathyroidectomy and some elderly patients may refuse surgery for various reasons including perceived risk.[1,9] In the present study, all of the patients were treated with calcimimetics because they refused to undergo parathyroidectomy or were unsuitable for parathyroidectomy.

PHPT is associated with an increased set point for calcium-mediated PTH release.[19] The cause is thought to be dysfunction of the calcium-sensing receptor (CASR) in the parathyroid lesion, with which reduced CASR expression or loss-of-function *CASR* mutations may be associated.[20] Calcimimetics are CASR positive allosteric modulators that decrease parathyroid gland proliferation and PTH secretion.[20] Calcimimetics, including cinacalcet and evocalcet, are available for PHPT patients who are unable to undergo parathyroid surgery or who have postoperative recurrence of PHPT.[11,21] Both cinacalcet and evocalcet have been reported to improve hypercalcemia and hypophosphatemia but not bone loss in patients with PHPT.[10,11,22] Moreover, cinacalcet administration was reported to reduce the size of parathyroid adenomas in patients with PHPT.[23] Treatment with calcimimetics, especially cinacalcet, may lead to upper gastrointestinal adverse events such as vomiting and nausea.[11,22] In the present study, two of the nine patients had appetite loss possibly due to the administration of calcimimetics.

In patients with PHPT, BMD at cancellous sites including the lumbar spine is preserved, while that at cortical sites including the femoral neck is decreased.[5] It is considered that the catabolic effects of PTH has a greater influence on cortical bone than on cancellous bone.[5] Since alendronate increases BMD in PHPT patients, it may be useful for patients with bone loss who do not undergo parathyroidectomy.[24] Our previous study suggested that upregulated vitamin D activity, estimated by the serum $1,25(OH)_2D/25(OH)D$ ratio, might be associated with disruption of bone metabolism,[25] and the increased serum $1,25(OH)_2D/25(OH)D$ ratio in the present study may be related to bone loss in PHPT patients. Urinary cAMP excretion and nephrogenous cAMP level are known to be elevated in patients with PHPT, reflecting the effect of oversecreted PTH.[26] Our study showed that there was a high level of nephrogenous cAMP in PHPT patients and that urinary cAMP was negatively correlated with reduction rate of serum cCa level by calcimimetic treatment. Nephrogenous cAMP, which is a marker of PTH activity, is obtained by subtracting plasma cAMP from urinary cAMP. The present study newly suggested that urinary cAMP, and nephrogenous cAMP, is associated with calcium metabolism in elderly PHPT patients receiving calcimimetic treatment. However, the precise mechanism underlying the correlation between cAMP metabolism and effects of calcimimetics remains unknown. Taking all of the data into consideration, administration of calcimimetics might be effective for reduction of elevated serum cCa levels in PHPT patients who have been exposed to quite high levels of PTH for a relatively long time.

This study focused on short-term effects of calcimimetics for PHPT patients, and relevance of the long-term effects to clinical characteristics remains to be elucidated. Previous studies showed that it took three months for elevated serum cCa levels to be reduced to levels maintained by the administration of cinacalcet[22] or evocalcet,[11] while our follow-up duration was relatively short (about three weeks). This case series included mainly female PHPT patients (8 females and one male), and gender was considered to be a confounding factor. Moreover, bisphosphonates used for osteoporosis in the present study are conceivably another confounding factor, since bisphosphonates affect calcium metabolism. Another limitation of this study is that the study was performed retrospectively at a single center. Data were analyzed for a very limited number of PHPT patients, since surgical

indication is firstly recommended for all PHPT patients. Therefore, a larger sample size of PHPT patients including a sufficient number of both genders with relatively long-term follow-up is needed in a further study.

In summary, the present study indicated that elevated serum cCa levels may be reduced by calcimimetic treatment more effectively in PHPT patients of relatively advanced age, patients with low DEXA %YAM, and patients with low urinary cAMP.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

KY wrote the first draft and managed all of the submission process. YN and KT performed data collection. HH and KH contributed to the clinical management of the patient. AS, HO, MO, and YH supervised the study. FO organized the manuscript.

ETHICAL APPROVAL

Written informed consent was obtained from the patients to publish this report in accordance with the journal's patient consent policy.

CONSENT

Written informed consent was obtained from the patients to publish this report.

DATA AVAILABILITY STATEMENT

The data are available on request due to privacy/ethical restrictions.

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How to cite this article: Yamamoto K, Nakano Y, Tokumasu K, et al. Relationship between patients' characteristics and efficacy of calcimimetics for primary hyperparathyroidism in the elderly. *Clin Case Rep*. 2022;10:e05713. doi:10.1002/ccr3.5713