Reduction in parathyroid adenomas by cinacalcet therapy in patients with primary hyperparathyroidism

Midori Minezaki[1#], Yuichi Takashi[1,2#*], Kentaro Ochi[1], Ryo Mitsuoka[1,2], Yuka Yamao[1], Tadachika Kudo[1], Daiji Kawanami[2], Kunihisa Kobayashi[1], Ichiro Abe[1]

[#] These authors contributed equally to this work.

[1]Department of Endocrinology and Diabetes Mellitus, Fukuoka University Chikushi Hospital, Chikushino, Japan.

[2]Department of Endocrinology and Diabetes Mellitus, Fukuoka University School of Medicine, Fukuoka, Japan.

*Correspondence: Yuichi Takashi

E-mail: y.takashi.si@fukuoka-u.ac.jp

Address: Department of Endocrinology and Diabetes Mellitus, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jyonan-ku, Fukuoka City, 814-0180 Fukuoka, Japan

Phone: +81-92-801-1011

"This is a post-peer-review,pre-copyedit version of an article published in ［J Bone Miner Metab］.
The final authenticated version is available online at:https://dx.doi.org/［10.1007/s00774-020-01190-2］".

Abstract

Introduction

Cinacalcet is a calcimimetic that modulates the functions of calcium-sensing receptor and is currently used to treat patients with primary hyperparathyroidism (PHPT). Although it was reported that cinacalcet treatment reduced the size of hyperplastic parathyroid glands in patients with secondary hyperparathyroidism, whether or not cinacalcet treatment can reduce the size of parathyroid adenomas in patients with PHPT has been unknown.

Materials and methods

We recruited nine (male: one, female: eight) patients with PHPT due to parathyroid adenomas who did not undergo parathyroidectomy. Cinacalcet was administered at a dose of 50 mg/day, and we evaluated the size of parathyroid adenomas (width × thickness) (mm^2) using ultrasonography before and after 6 months of cinacalcet treatment.

Results

The mean age of the subjects was 58.1 ± 7.2 years old, and the mean serum intact parathyroid hormone (PTH) concentration was 134.8 ± 8.7 pg/ml. All participants showed hypercalcemia and osteopenia. After 6 months, the mean size of parathyroid adenomas was significantly decreased (baseline: 73.8 ± 33.4 mm^2 vs. after 6 months: 52.5 ± 25.0 mm^2, $p = 0.045$). Thus, 6-month cinacalcet treatment induced a 29% size reduction in parathyroid adenomas. Furthermore, the serum intact PTH concentration before cinacalcet treatment was positively correlated with the reduction in the size of parathyroid adenomas.

Conclusion

The present study revealed that cinacalcet treatment reduces the size of parathyroid adenomas in patients with PHPT. The accumulation of more PHPT cases with cinacalcet therapy is required to confirm this finding.

Keywords

Cinacalcet, Primary hyperparathyroidism, Parathyroid adenoma

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder [1-4]. Most patients with PHPT are diagnosed incidentally because of the absence of typical findings, but some patients show symptoms caused by hypercalcemia and high bone turnover. PHPT is more common in postmenopausal women than in men and premenopausal women [2]. Excessive secretion of parathyroid hormone (PTH) in patients with PHPT causes hypercalcemia, hypercalciuria, urolithiasis and osteoporosis [5]. Most PHPT are caused by parathyroid adenoma, while others are caused by parathyroid hyperplasia and parathyroid cancer [6]. Regarding patients with PHPT due to parathyroid adenoma, parathyroidectomy (PTX) is the only definitive therapy at present [7-11]. However, several patients with PHPT are medically unfit for surgical therapy, while others refuse the surgery for various reasons.

Cinacalcet was first approved for patients with secondary hyperparathyroidism (SHPT), and it has recently become available as a treatment for patients with PHPT who are not suitable for surgery. Cinacalcet is a calcimimetic that modulates the functions of calcium-sensing receptor (CaSR) and reduces the PTH secretion from parathyroid glands [12]. Cinacalcet is useful for treating hypercalcemia but is ineffective for correcting abnormal bone metabolism in patients with PHPT [13]. Regarding cases of SHPT, several previous reports have indicated that cinacalcet reduces the size of hyperplastic parathyroid glands [14-18]. However, there have been no reports examining whether or not cinacalcet can reduce the size of parathyroid adenomas in patients with PHPT.

Given the above, we investigated the effect of cinacalcet treatment on the reduction in the size of parathyroid adenomas in patients with PHPT.

Materials and methods

Ethical approval of the study protocol

The study protocol was approved by the research ethics committee of Fukuoka University Chikushi Hospital (#C20-05-006).

Subjects

This study was performed as a retrospective cohort study. We recruited nine patients with PHPT at Fukuoka University Chikushi Hospital from April 2014 to February 2020. All subjects were diagnosed with PHPT due to parathyroid adenoma but did not undergo PTX either because of rejection of surgery or religious objections. All participants were free from anti-osteoporotic agents, including vitamin D preparations, during the study period. In addition, we confirmed that no participants had started taking any type of dietary supplement, including native vitamin D.

Study design

The subjects were administered cinacalcet at a dose of 50 mg/day, but in 3 patients, the doses were reduced to 25 mg/day due to adverse effects, such as hypocalcemia, numbness of the hands and nausea. We evaluated the size of parathyroid adenomas using 8-MHz ultrasonography (Aplio300; Canon, Tochigi, Japan) before and after 6-month treatment. Concerning the size of parathyroid adenomas in the present study, the 2-dimensional size (width × thickness) (mm^2) on a cross-echo image by 1 fixed sonographer was used as an index.

In addition, we also examined related parameters. The serum intact PTH concentration was measured by an electro chemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Tokyo, Japan). Serum concentrations of calcium, phosphate, urea nitrogen, creatinine and albumin and urine concentrations of calcium, phosphate and creatinine were measured using

an autoanalyzer (BioMajesty; JEOL, Tokyo, Japan). The serum calcium concentration was corrected for albumin. The bone mineral density (BMD) of the femoral neck and lumbar spine was evaluated by dual-energy X-ray absorptiometry (Discovery; Hologic Japan, Tokyo, Japan).

Statistical analyses

Data are described as the mean ± standard error of the mean. Differences between baseline and six months after cinacalcet treatment were estimated by a paired Student's *t*-test. Correlations between the size change of parathyroid adenomas and each parameter were evaluated by Pearson's correlation coefficients. Statistical analyses were performed using the BellCurve 3.21 software program (SSRI, Tokyo, Japan). Statistical tests were two-sided, and a p value of < 0.05 was considered statistically significant.

Results

The clinical characteristics of the subjects are shown in Table 1. The mean age was 58.1 ± 7.2 years old, and 1 male and 8 females were included in this study. Corrected serum calcium and serum phosphate concentrations were 10.8 ± 0.4 mg/dl and 2.4 ± 0.2 mg/dl, respectively. The serum intact PTH concentration was 134.8 ± 8.7 pg/ml, and BMD evaluations showed osteopenia in both the femoral neck and lumbar spine. The size of parathyroid adenomas evaluated by ultrasonography was 73.8 ± 33.4 mm^2. All participants underwent technetium-99m sestamibi (^{99m}Tc-MIBI) scintigraphy before this study. Ultrasonography and scintigraphy produced the same results concerning the localization of parathyroid adenomas in six patients. In addition, we ruled out the possibility of SHPT for all participants.

After six-month treatment, the mean corrected serum calcium and serum intact PTH concentrations were significantly decreased, and the serum phosphate concentration was significantly increased (Table 1). In contrast, the mean BMD of the femoral neck and lumbar spine did not change markedly from the baseline (Table 1). At that time, the mean size of parathyroid adenomas was decreased (baseline: 73.8 ± 33.4 mm^2 vs. after 6 months: 52.5 ± 25.0 mm^2, $p = 0.045$) (Table 1 and Fig. 1A). Therefore, 6-month cinacalcet treatment induced a significant 29% size reduction in parathyroid adenomas (Fig. 1B). All images of the subjects are shown in Fig. 2.

We then examined the parameters correlated with the size change in parathyroid adenomas induced by cinacalcet treatment. The serum intact PTH concentration before cinacalcet treatment was significantly correlated with the reduction in the size of parathyroid adenomas (Table 2 and Fig. 3). In fact, the patient who showed the most effectiveness in shrinkage of parathyroid adenoma had the lowest serum intact PTH concentration before cinacalcet treatment, and the patient who did not show reduction in parathyroid adenoma had the second-highest serum intact PTH concentration, as shown Fig. 3. However, no other

parameters were correlated with the reduction in the size of parathyroid adenomas (Table 2). Furthermore, the changes in the parameters after six-month treatment were not correlated with the reduction in the size of parathyroid adenomas (Table 2).

Discussion

Cinacalcet acts as an allosteric modulator of CaSR and enhances the sensitivity of CaSR to extracellular calcium while reducing the PTH secretion from parathyroid glands [19]. It was indicated that cinacalcet is effective in lowering the serum intact PTH concentration and concomitantly inducing a reduction in hyperplastic parathyroid glands in moderate to severe SHPT, even in patients with enlarged parathyroid glands [14-16]. In experimental settings, it was reported that decreased blood flow, cystic changes, hemorrhagic changes and improved hypertrophy were observed in hyperplastic parathyroid glands following cinacalcet administration to rat models of renal failure [20]. Imanishi et al. showed that cinacalcet suppresses parathyroid cell proliferation without affecting apoptosis in a murine model of PHPT [21]. However, increased parathyroid cell apoptosis has been demonstrated in surgically removed parathyroid glands from patients with SHPT who received cinacalcet treatment before surgery [22]. Thus, the precise mechanism underlying the reduction in the size of hyperplastic parathyroid glands induced by cinacalcet treatment remains unknown. The present study is the first to examine whether or not cinacalcet treatment reduces the size of parathyroid adenomas in patients with PHPT, and the results indicate that cinacalcet treatment does indeed induce the size reduction in parathyroid adenomas in patients with PHPT.

Next, we wondered in what kind of patients with PHPT is cinacalcet treatment most effective at inducing shrinkage of parathyroid adenomas. In the present study, patients with lower serum intact PTH concentration before cinacalcet treatment showed a greater reduction in parathyroid adenomas than those with higher concentrations. Regarding SHPT, Ichii et al. reported that the size of hyperplastic parathyroid glands before cinacalcet treatment was correlated with the size reduction by cinacalcet treatment [15]. Komaba et al. indicated that cinacalcet treatment reduces the size of hyperplastic parathyroid glands, regardless of pretreatment gland sizes, in patients with SHPT, but the degree of size reduction seems to be

more pronounced in patients with greater parathyroid hyperplasia at baseline than in those with less-marked hyperplasia [16]. Which parameters best correlate with the size reduction in parathyroid adenomas or hyperplastic parathyroid glands has been unclear.

Although cinacalcet was initially expected to improve bone metabolism in patients with PHPT, its performance in clinical trials has not been impressive [13, 23, 24]. In the present study, no improvement in the BMD was observed, similar to findings in previous studies.

Several limitations associated with the present study warrant mention. First, the present investigation was a single-center retrospective study and thus had a small number of cases and short duration. In addition, this was an open-label and single-arm study without a concurrent control group. Generally, the male-to-female ratio of PHPT patients is 1:3, but the actual ratio was 1:8 in our study. Second, we were unable to evaluate the size of parathyroid adenomas as a three-dimensional volume because the longitudinal diameter had not been measured in some cases. Third, vitamin D deficiency affects the pathophysiology of PHPT [25], but we were unable to estimate vitamin D deficiency before cinacalcet treatment. However, vitamin D deficiency was observed in all cases after the study period.

In conclusion, the present study revealed that cinacalcet treatment reduces the size of parathyroid adenomas in patients with PHPT. The accumulation of more PHPT cases with cinacalcet therapy is required to confirm this finding.

Acknowledgements

The authors thank Prof. Seiji Fukumoto (Tokushima University) for his great advice concerning the present study. We also thank Ms. Yumi Iriguchi for her secretarial assistance.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Adami S, Marcocci C, Gatti D (2002) Epidemiology of primary hyperparathyroidism in Europe. J Bone Miner Res 17 Suppl 2:N18-23
2. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton LJ, 3rd (2006) Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. J Bone Miner Res 21:171-177
3. Yu N, Donnan PT, Murphy MJ, Leese GP (2009) Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. Clin Endocrinol (Oxf) 71:485-493
4. Yeh MW, Ituarte PH, Zhou HC, Nishimoto S, Liu IL, Harari A, Haigh PI, Adams AL (2013) Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab 98:1122-1129
5. Insogna KL (2018) Primary Hyperparathyroidism. N Engl J Med 379:1050-1059
6. Udelsman R (2002) Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. Ann Surg 235:665-670; discussion 670-662
7. Chan AK, Duh QY, Katz MH, Siperstein AE, Clark OH (1995) Clinical manifestations of primary hyperparathyroidism before and after parathyroidectomy. A case-control study. Ann Surg 222:402-412; discussion 412-404
8. Talpos GB, Bone HG, 3rd, Kleerekoper M, Phillips ER, Alam M, Honasoge M, Divine GW, Rao DS (2000) Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey. Surgery 128:1013-1020
9. Vestergaard P, Mosekilde L (2003) Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. BMJ 327:530-534
10. Rao DS, Phillips ER, Divine GW, Talpos GB (2004) Randomized controlled clinical

trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab 89:5415-5422

11. (2005) The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism. Endocr Pract 11:49-54

12. Kawata T, Imanishi Y, Kobayashi K, Onoda N, Okuno S, Takemoto Y, Komo T, Tahara H, Wada M, Nagano N, Ishimura E, Miki T, Ishikawa T, Inaba M, Nishizawa Y (2006) Direct in vitro evidence of the suppressive effect of cinacalcet HCl on parathyroid hormone secretion in human parathyroid cells with pathologically reduced calcium-sensing receptor levels. J Bone Miner Metab 24:300-306

13. Peacock M, Bolognese MA, Borofsky M, Scumpia S, Sterling LR, Cheng S, Shoback D (2009) Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. J Clin Endocrinol Metab 94:4860-4867

14. Meola M, Petrucci I, Barsotti G (2009) Long-term treatment with cinacalcet and conventional therapy reduces parathyroid hyperplasia in severe secondary hyperparathyroidism. Nephrol Dial Transplant 24:982-989

15. Ichii M, Ishimura E, Okuno S, Chou H, Kato Y, Tsuboniwa N, Nagasue K, Maekawa K, Yamakawa T, Inaba M, Nishizawa Y (2010) Decreases in parathyroid gland volume after cinacalcet treatment in hemodialysis patients with secondary hyperparathyroidism. Nephron Clin Pract 115:c195-202

16. Komaba H, Nakanishi S, Fujimori A, Tanaka M, Shin J, Shibuya K, Nishioka M, Hasegawa H, Kurosawa T, Fukagawa M (2010) Cinacalcet effectively reduces parathyroid hormone secretion and gland volume regardless of pretreatment gland size in patients with secondary hyperparathyroidism. Clin J Am Soc Nephrol 5:2305-2314

17. Nagano N (2006) Pharmacological and clinical properties of calcimimetics: calcium

receptor activators that afford an innovative approach to controlling hyperparathyroidism. Pharmacol Ther 109:339-365

18. Sumida K, Nakamura M, Ubara Y, Marui Y, Tanaka K, Takaichi K, Tomikawa S, Inoshita N, Ohashi K (2011) Histopathological alterations of the parathyroid glands in haemodialysis patients with secondary hyperparathyroidism refractory to cinacalcet hydrochloride. J Clin Pathol 64:756-760

19. Nemeth EF, Heaton WH, Miller M, Fox J, Balandrin MF, Van Wagenen BC, Colloton M, Karbon W, Scherrer J, Shatzen E, Rishton G, Scully S, Qi M, Harris R, Lacey D, Martin D (2004) Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. J Pharmacol Exp Ther 308:627-635

20. Colloton M, Shatzen E, Miller G, Stehman-Breen C, Wada M, Lacey D, Martin D (2005) Cinacalcet HCl attenuates parathyroid hyperplasia in a rat model of secondary hyperparathyroidism. Kidney Int 67:467-476

21. Imanishi Y, Kawata T, Kenko T, Wada M, Nagano N, Miki T, Arnold A, Inaba M (2011) Cinacalcet HCl suppresses Cyclin D1 oncogene-derived parathyroid cell proliferation in a murine model for primary hyperparathyroidism. Calcif Tissue Int 89:29-35

22. Tatsumi R, Komaba H, Kanai G, Miyakogawa T, Sawada K, Kakuta T, Fukagawa M (2013) Cinacalcet induces apoptosis in parathyroid cells in patients with secondary hyperparathyroidism: histological and cytological analyses. Nephron Clin Pract 124:224-231

23. Keutgen XM, Buitrago D, Filicori F, Kundel A, Elemento O, Fahey TJ, 3rd, Zarnegar R (2012) Calcimimetics versus parathyroidectomy for treatment of primary hyperparathyroidism: retrospective chart analysis of a prospective database. Ann Surg 255:981-985

24. Nemeth EF, Goodman WG (2016) Calcimimetic and Calcilytic Drugs: Feats, Flops,

and Futures. Calcif Tissue Int 98:341-358

25. Rao DS, Honasoge M, Divine GW, Phillips ER, Lee MW, Ansari MR, Talpos GB, Parfitt AM (2000) Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications. J Clin Endocrinol Metab 85:1054-1058

Figure legends

Fig. 1 Cinacalcet treatment in patients with PHPT reduces the size of parathyroid adenomas. The size of parathyroid adenomas was decreased (baseline: 73.8 ± 33.4 mm^2 vs. after six months: 52.5 ± 25.0 mm^2, $p = 0.045$ by paired Student's *t*-test) (A). The reduction rate of parathyroid adenomas was shown, and cinacalcet induced a significant 29% size reduction (B).

Fig. 2 Ultrasonography of parathyroid adenomas. All images of the subjects are shown. The left side shows the condition before cinacalcet treatment, while the right side shows the condition after six months. Calculated sizes of parathyroid adenomas (mm^2) are shown below each image.

Fig. 3 Patients with low serum intact PTH concentrations before cinacalcet treatment showed a greater reduction in parathyroid adenomas than in those with high concentrations. The serum intact PTH concentration before cinacalcet treatment was significantly correlated with the reduction in the size of parathyroid adenomas ($r = 0.84$, $p < 0.01$ by Pearson's correlation coefficient).

Table 1 Clinical characteristics of the subjects at baseline and six months after cinacalcet treatment

	Baseline	After six months	*p* value
Age (years)	58.1 ± 7.2	-	-
Gender (male/female)	1 / 8	-	-
Body mass index (kg/m^2)	23.9 ± 1.3	-	-
Corrected serum calcium (mg/dl)	10.9 ± 0.5	9.2 ± 0.3	<0.01*
Serum phosphate (mg/dl)	2.4 ± 0.2	3.1 ± 0.1	<0.01*
Serum intact PTH (pg/ml)	134.8 ± 8.7	97.3 ± 14.1	0.025*
Serum urea nitrogen (mg/dl)	14.7 ± 1.4	16.0 ± 1.7	0.36
Serum creatinine (mg/dl)	0.67 ± 0.07	0.73 ± 0.07	0.11
eGFR (ml/min/1.73m^2)	79.8 ± 8.9	73.0 ± 9.1	0.07
Urine calcium (mg/dl)	12.4 ± 7.1	-	-
Urine phosphate (mg/dl)	48.6 ± 42.1	-	-
Urine creatinine (mg/dl)	69.9 ± 31.5	-	-
BMD of femoral neck (T-score)	-2.0 ± 0.3	-1.6 ± 0.5	0.58
BMD of lumbar spine (T-score)	-2.0 ± 0.3	-1.7 ± 0.6	0.32
Size of parathyroid adenoma (mm^2)	73.8 ± 33.4	52.5 ± 25.0	0.045*

* Statistically significant (p value < 0.05)

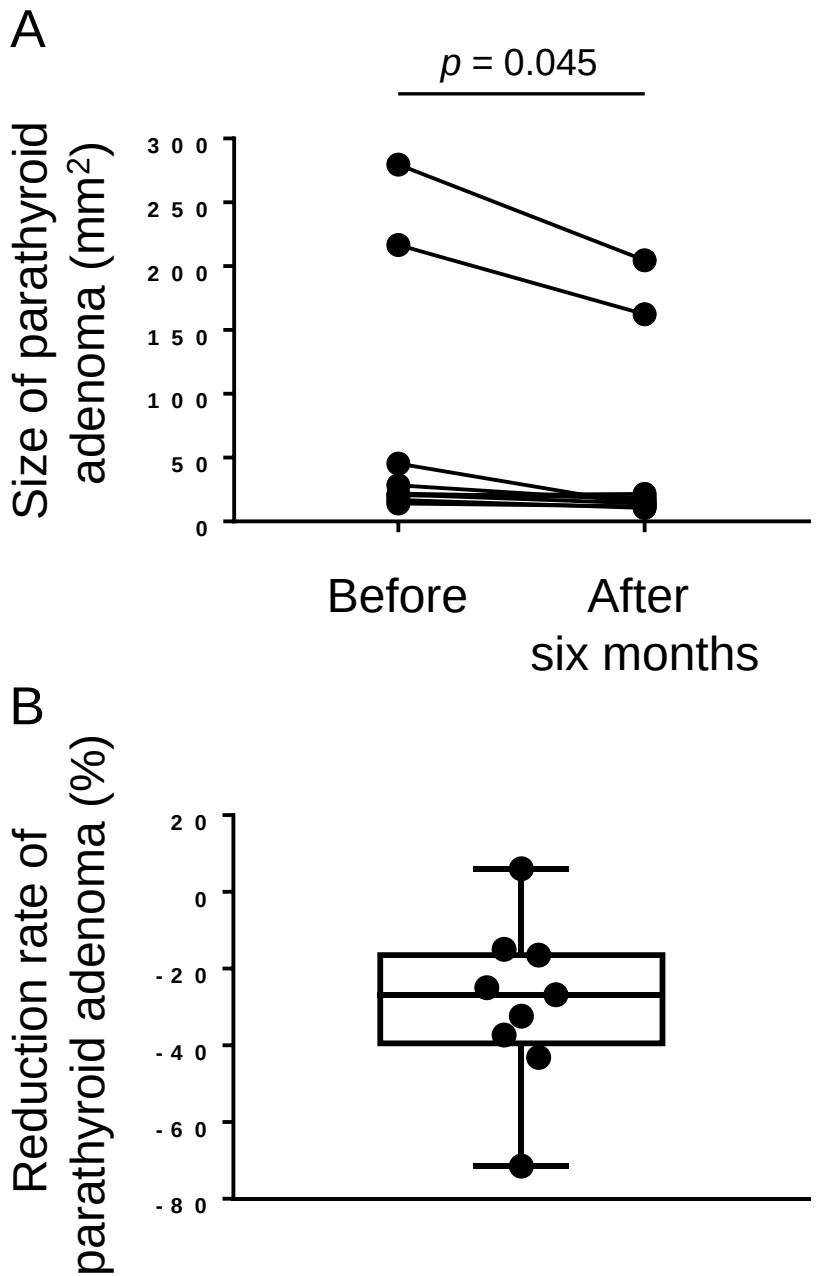
PTH parathyroid hormone, *eGFR* estimated glomerular filtration rate, *BMD* bone mineral density

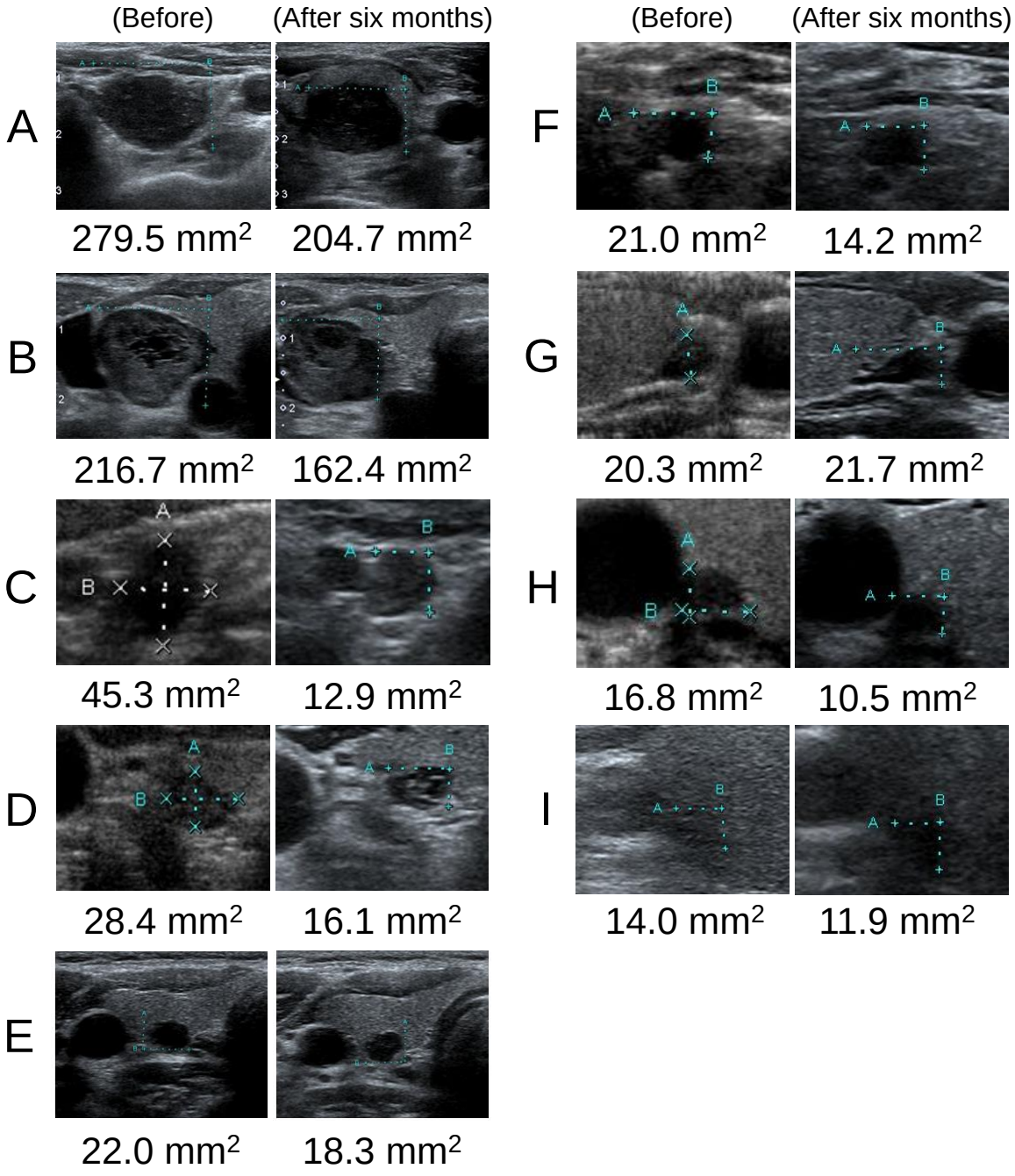
Table 2 Correlations between the size change of parathyroid adenomas and each parameter

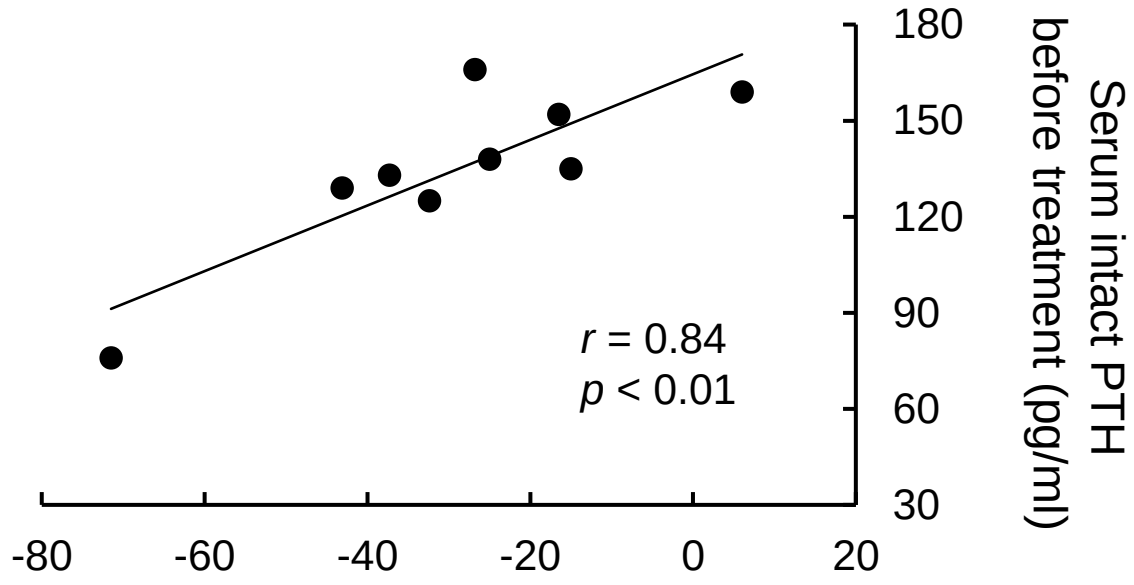
	Baseline		*Δ* (after six months-baseline)	
	r	*p* value	*r*	*p* value
Age (years)	-0.35	0.36	-	-
Body mass index (kg/m^2)	-0.05	0.89	-	-
Corrected serum calcium (mg/dl)	0.39	0.30	0.11	0.78
Serum phosphate (mg/dl)	-0.45	0.22	0.46	0.22
Serum intact PTH (pg/ml)	0.84	<0.01*	0.19	0.62
Serum urea nitrogen (mg/dl)	-0.44	0.24	-0.32	0.39
Serum creatinine (mg/dl)	0.18	0.64	0.48	0.19
eGFR (ml/min/1.73m^2)	0.03	0.94	-0.52	0.15
Urine calcium (mg/dl)	0.15	0.70	-	-
Urine phosphate (mg/dl)	-0.19	0.62	-	-
Urine creatinine (mg/dl)	-0.18	0.63	-	-
BMD of femoral neck (T-score)	-0.32	0.39	0.26	0.51
BMD of lumbar spine (T-score)	0.40	0.32	0.26	0.54
Size of parathyroid adenoma (mm^2)	0.01	0.98	-	-

* Statistically significant (p value < 0.05)

PTH parathyroid hormone, *eGFR* estimated glomerular filtration rate, *BMD* bone mineral density


A
p = 0.045
Size of parathyroid adenoma (mm2)
300
250
200
150
100
50
0
Before
After six months
B
Reduction rate of parathyroid adenoma (%)
20
0
-20
-40
-60
-80


(Before)
(After six months)
(Before)
(After six months)
A
279.5 mm2
204.7 mm2
F
21.0 mm2
14.2 mm2
B
216.7 mm2
162.4 mm2
G
20.3 mm2
21.7 mm2
C
45.3 mm2
12.9 mm2
H
16.8 mm2
10.5 mm2
D
28.4 mm2
16.1 mm2
I
14.0 mm2
11.9 mm2
E
22.0 mm2
18.3 mm2


180
150
120
90
60
30
Serum intact PTH
before treatment (pg/ml)
r = 0.84
p < 0.01
-80
-60
-40
-20
0
20
Reduction rate of parathyroid adenoma (%)