J Bone Miner Metab (2007) 25:226–231
DOI 10.1007/s00774-007-0754-z

ORIGINAL ARTICLE

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Remarkable increase in lumbar spine bone mineral density and amelioration in biochemical markers of bone turnover after parathyroidectomy in elderly patients with primary hyperparathyroidism: a 5-year follow-up study

Received: August 15, 2006 / Accepted: February 27, 2007

Abstract We evaluated the efficacy of parathyroidectomy (PTX) on bone mineral density (BMD) and hormonal and biochemical markers of bone metabolism in elderly primary hyperparathyroidism (PHPT) patients, and followed these patients for 5 years after PTX. Eleven PHPT patients were enrolled and were followed for 5 years by measuring lumbar spine BMD (LSBMD), femoral BMD (FBMD), radial BMD (RBMD), parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], serum calcium (SCa), inorganic phosphate (iP), bone-specific alkaline phosphatase (BAP), intact osteocalcin (IOC), urinary excretion of type I collagen cross-linked N-telopeptide (NTx), and urinary deoxypyridinoline (DPD). PTX produced significant increases in LSBMD of 12%, 19%, and 29% as compared with pretreatment levels after 1, 3, and 5 years, respectively ($P < 0.01$, compared to baseline), whereas there was no significant increase in FBMD and a slight decrease in RBMD. SCa and iP levels remained normal over the five years. PTX also resulted in significant decreases in PTH, 1,25$(OH)_2$D, BAP, IOC, NTx, and DPD that continued for at least 3 years after PTX. In conclusion, PTX seemed effective to normalize various markers of bone metabolism in elderly PHPT patients and is recommended to patients with low LSBMD to prevent future fractures. On the other hand, the use of PTX for low FBMD or RBMD patients requires further discussion.

Key words primary hyperparathyroidism (PHPT) · parathyroidectomy (PTX) · bone mineral density (BMD) · elderly

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Introduction

Progressive parathyroid hormone-dependent bone loss is a risk factor for fractures in patients with primary hyperparathyroidism (PHPT) [1]. Especially, elderly PHPT patients have a higher risk of fractures than younger patients [2]. Guo et al. reported significant bone loss and decreases in bone mineral density (BMD) in untreated postmenopausal women with PHPT in total body and femoral neck evaluations [3]. Several studies [4,5] and case reports [6] have shown that parathyroidectomy (PTX) can improve BMD in PHPT patients. Silverberg et al. investigated the effect of PTX on BMD change in a prospective study and found that patients who underwent PTX experienced a normalization of biochemical bone formation/resorption markers and increased BMD in lumbar spine (LS) and femoral neck (FN) evaluations 4 years post-PTX [4], and even after follow-up for 10 years [5]. These reports indicate the effectiveness of surgical treatment for PHPT patients.

However, most of these studies involve relatively young patients with a mean age of about 50 years. There have been few long-term studies exploring the efficacy of PTX for the treatment of elderly PHPT patients. Recently, we showed that PTX produces a significant increase in lumbar spine BMD (LSBMD) of 20% compared to pretreatment levels 1 year after treatment in elderly women with PHPT, an effect that was twice that of intermittent etidronate administration [7]. We here report the results of a longitudinal, 5-year follow-up study to evaluate improvements in BMD produced by PTX treatment in elderly PHPT patients.

Patients and methods

Eleven patients with an average age of 72.7 ± 8.5 years (range, 61–84 years) who underwent PTX between 1998 and 2002 were enrolled in the follow-up study. The diagnosis of PHTP was made by measuring serum calcium levels and intact PTH (1–84PTH) concentrations, and by cervical

echography, computed tomography and ^{99m}Tc-MIBI scintigraphy, which confirmed the localization of parathyroid adenoma. The decision to recommend PTX was made based on guidelines adopted by the NIH Consensus Conference [8]. For these patients, BMD and the biochemical markers listed below were measured before and 1, 3, and 5 years after PTX, except for intact PTH and $1,25(OH)_2D$, for which postoperative data were collected for only 3 years. The protocol was approved by the Tokyo Metropolitan Geriatric Hospital Ethical Committee; informed consent was obtained from all subjects.

LSBMD (anteroposterior; L2–L4), total femoral BMD (FBMD), and distal one-third of the radial BMD (RBMD) were measured by dual-energy X-ray absorptiometry (DXA; Lunar DPX-L, Madison, Lunar, WI, USA). The Z-scores and T-scores were calculated for each portion and used for statistical analysis. Lumbar X-ray photography was performed to detect vertebral fractures. The precision of DPX-L was 0.7% in CV. The Z-score is the number of SD a given measurement differs from the mean for a sex- and age-matched reference population. The T-score is the number of SD by which a given measurement differs from the mean for a normal young adult reference population.

Intact parathyroid hormone (1–84PTH) levels were measured by an immunoradiometric assay (IRMA; Allegro Intact PTH, Nichols Institute, San Juan, Capistrano, CA, USA) [9]. 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] was assayed by a radioimunnoassay (RIA) (Immunodiagnostic Systems, Boldon, England) [10]. Interassay and intraassay variances for PTH and $1,25(OH)_2D$ were 4.3% and 8.5%, and 9.8% and 13.8%, respectively.

Serum levels of total calcium, inorganic phosphate, albumin, and alkaline phosphatase were measured in the hospital laboratory by standard methods using a Toshiba autoanalyzer (Toshiba, Tokyo, Japan). Serum calcium was adjusted for serum albumin by Payne's method.

Biochemical markers of bone turnover were measured as previously described [11]. Intact osteocalcin (IOC) was assayed by an IRMA, and urinary excretion of type I collagen cross-linked N-telopeptide (NTx) was measured by enzyme-linked immunosorbent assay (ELISA) (Kokusai Seiyaku, Kobe, Japan). Free urinary deoxypyridinoline (DPD) levels were measured in morning void urine samples with Osteolinks DPD assay kits (Quidel, San Diego, CA, USA). Intraassay and interassay variances of IOC were 4.3% and 2.8%; intraassay and interassay variances of NTx and DPD were 3.1% and 3.0%, and 5.0% and 6.8%, respectively.

The longitudinal changes in BMD, calciotropic hormones, and all other biochemical markers were first evaluated by repeated analysis of variance (ANOVA), and values at each time point were compared with the baseline level by paired *t* test.

Results

Patient profiles at entry (just before surgery) are shown in Table 1. The mean age was 72.7 ± 8.5 years (range, 61–84 years), and 8 of the 11 subjects (73%) were women, all of whom were postmenopausal. Four patients had suffered from vertebral fractures. Some data were deficient in BMD, Z-score, and T-score of femur and radius, and in intact PTH, $1,25(OH)_2D$, bone-specific alkaline phosphatase (BAP), IOC, NTx, and DPD; the available numbers (*n*) are 6 to 10.

None of the patients received bisphosphonates before or after PTX. However, four patients started taking active vitamin D_3 (alfacalcidol or calcitriol) soon after surgery, two patients began treatment with calcium aspartate, and two patients used both. These drugs were administered continuously in unchanged doses through the follow-up period.

During the follow-up period, none of the patients suffered new fractures. LSBMD and T-scores increased significantly 1 year after PTX, and the effect was still observed

Table 1. Baseline characteristics of patients

Age (years)	72.7 ± 8.5 (61–84)
Sex (male/female)	3/8
Height (cm)	150.5 ± 6.9
Body weight (kg)	48.7 ± 12.2
Body mass index (kg/m^2)	21.5 ± 4.9
Intact PTH (pmol/l) (*n* = 10)	17.2 ± 12.4
$1,25(OH)_2D$ (pmol/l) (*n* = 10)	133.7 ± 59.5
Serum Ca (mmol/l)	2.9 ± 0.3
Serum iP (mmol/l)	0.8 ± 0.2
BAP (IU/l) (*n* = 9)	49.6 ± 22.5
IOC (ng/dl) (*n* = 9)	21.7 ± 16.8
NTx (nMBCE/mMCr) (*n* = 9)	64.7 ± 19.6
DPD (nM/mMCr) (*n* = 10)	11.2 ± 5.1

	Lumbar (*n* = 11)	Femur (*n* = 7)	Radius (*n* = 6)
BMD (g/cm^2)	0.75 ± 0.30	0.61 ± 0.24	0.48 ± 0.19
Z-score	–0.90 ± 1.58	–0.20 ± 1.37	–0.85 ± 0.96
T-score	–3.14 ± 2.31	–2.07 ± 1.59	–3.18 ± 2.00

Postoperative medications
Active V D_3, 4; Ca, 2; both, 2

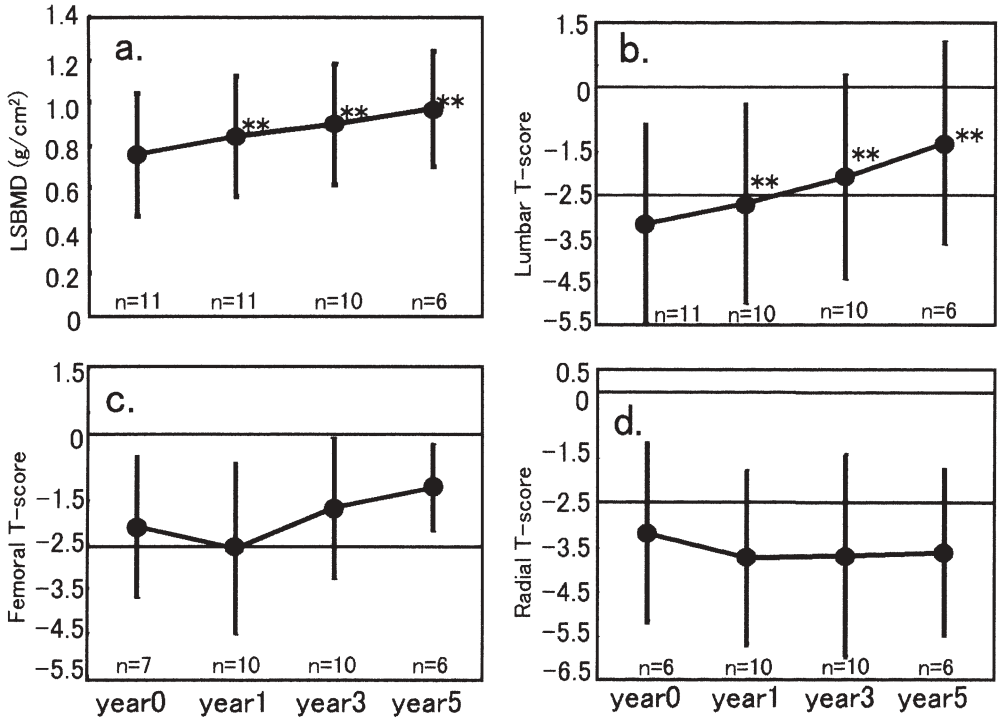

Fig. 1. Changes in lumbar spine bone mineral density (LSBMD, **a**) and changes in lumbar (**b**), femoral (**c**), and radial (**d**) T-scores. BMD at each site was measured before (*year0*), and 1 (*year1*), and 3 (*year3*), and 5 (*year5*) years parathyroidectomy after (PTX), and T-scores were calculated. Error bars indicate SD. $*P < 0.05$, $**P < 0.01$ versus year0 by paired *t* test

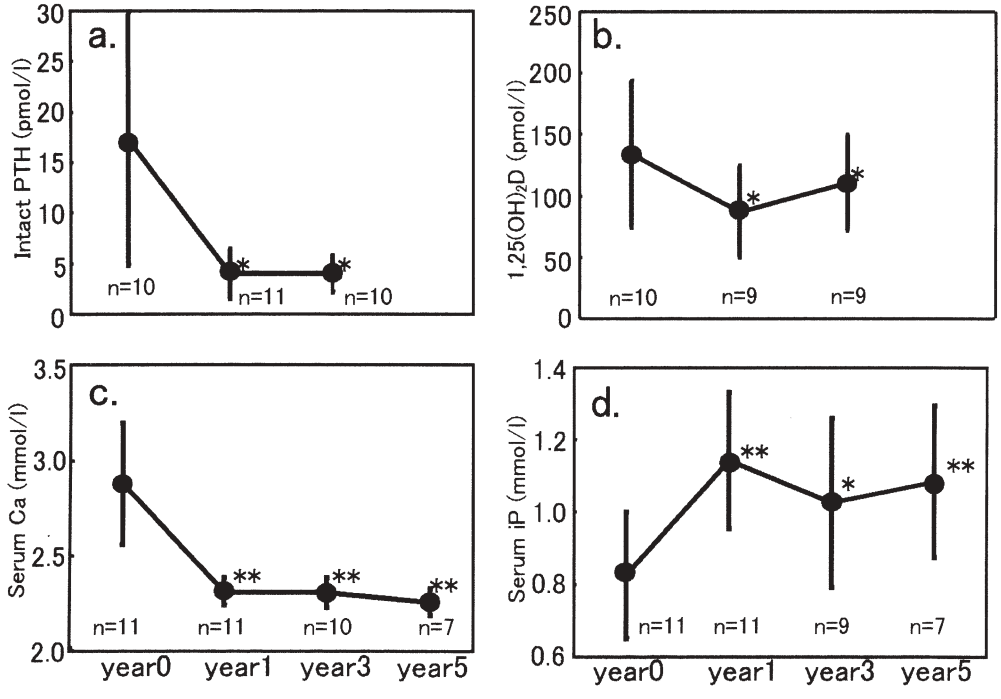

Fig. 2. Changes in calciotropic hormones and calcium. Intact parathyroid hormone (PTH) (**a**) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$, **b**) were followed for 3 years, and serum calcium (Ca, **c**) and serum inorganic phosphate (iP, **d**) were followed for 5 years after PTX. Error bars indicate SD. $*P < 0.05$, $**P < 0.01$ versus year0 by paired *t* test

after 5 years (Fig. 1a,b). LSBMD at 1 year (0.836 ± 0.296 g/cm^2) was increased by 12% as compared with the preoperative baseline level (0.748 ± 0.299 g/cm^2), and this increase extended linearly to 19% at 3 years (0.891 ± 0.300 g/cm^2) and 29% at 5 years (0.963 ± 0.292 g/cm^2) ($P < 0.01$). The T-score increased in parallel with LSBMD, from -3.143 ± 2.311 at baseline to -2.686 ± 2.325 after 1 year, and -2.080 ± 2.367 and -1.283 ± 2.351 after 3 and 5 years, respectively ($P < 0.01$). FBMD (baseline; 0.611 ± 0.235 g/cm^2) was also increased by 22% at 3 years (0.746 ± 0.202 g/cm^2) and by 27% at 5 years (0.831 ± 0.109 g/cm^2) after surgery. However, the increase in the T-score was not significant at any time during follow-up (Fig. 1c). In the radius, the RBMD (baseline, 0.476 ± 0.192 g/cm^2 vs. 5 years, 0.457 ± 0.167 g/cm^2) and the T-score decreased slightly (baseline, -3.183 ± 2.004 vs. 5 years, -3.633 ± 1.854) (Fig. 1d).

Changes in intact PTH and $1,25(OH)_2D3$ are shown in Fig. 2a and 2b, respectively. PTH levels decreased signifi-

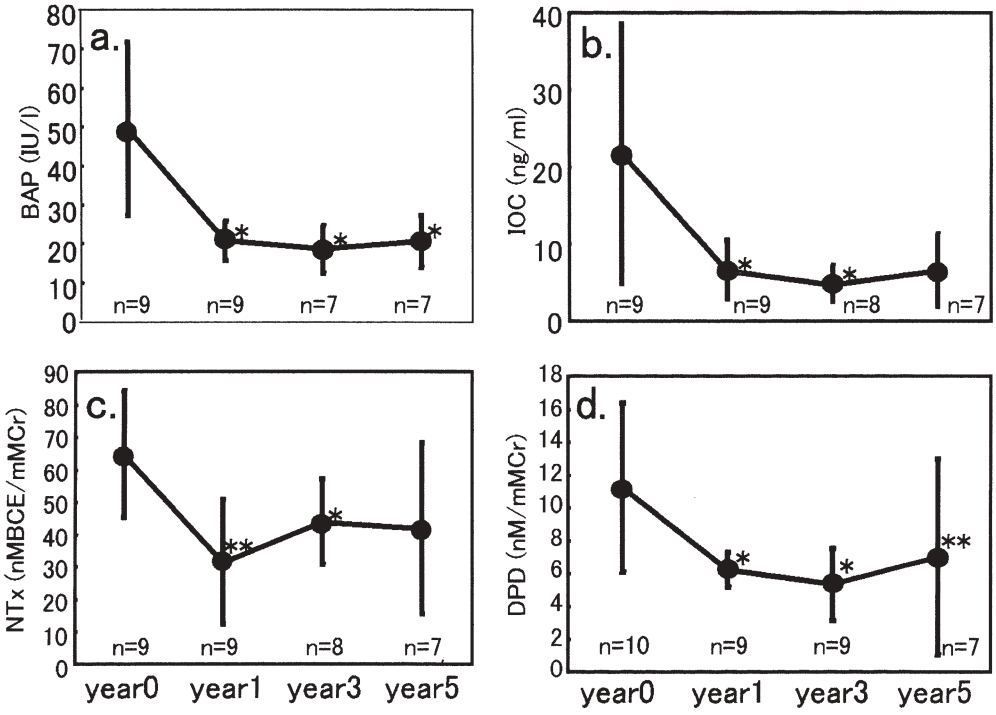

Fig. 3. Changes in biochemical markers of bone turnover. Bone-specific alkaline phosphatase (BAP, **a**), intact osteocalcin (IOC, **b**), urinary excretion of type I collagen cross-linked N-telopeptide (NTx, **c**), and urinary deoxy-pyridinoline (DPD, **d**) were measured before (year0), and at 1, 3, and 5 years after PTX. *BCE*, bone collagen equivalent; Cr, creatinine. Error bars indicate SD. $*P < 0.05$, $**P < 0.01$ versus year0 by paired *t* test

cantly, from 17.2 ± 12.4 to 4.0 ± 2.5 pmol/l after 1 year, and serum $1.25(OH)_2D3$ concentrations also fell from 133.7 ± 59.5 to 86.6 ± 37.2 pmol/l. Although the serum levels of these two hormones were followed for only 3 years after PTX, these changes remained significant for that period ($P < 0.01$). Total serum calcium levels decreased from 2.89 mmol/l to 2.32 mmol/l after 1 year, and further to 2.22 mmol/l after 5 years, whereas serum inorganic phosphate levels increased from 0.84 mmol/l to 1.13 mmol/l after 1 year and to 1.10 mmol/l after 5 years; both these changes were statistically significant as compared with preoperative levels ($P < 0.01$, Fig. 2c,d).

Figure 3 shows changes in bone formation and bone resorption markers during follow-up for 5 years. The levels of the bone formation marker serum alkaline phophatase decreased by 58% from the baseline level after 1 year ($P < 0.05$), and this suppressive effect was maintained at 5 years (Fig. 3a). Serum osteocalcin levels also declined by 70% after 1 year ($P < 0.05$), and this change was sustained up to 3 years. However, this reduction was no longer statistically significant at 5 years, although the absolute serum osteocalcin concentration was as low as at 1 year (Fig. 3b). As for bone resorption markers, NTx levels declined by 51%, 32%, and 36%, respectively, at 1 year, 3 years, and 5 years after PTX. The values at 1 year and 3 years were significantly lower than the pretreatment level ($P < 0.05$), whereas the difference at 5 years was not significant (Fig. 3c). DPD levels were significantly lower, by 45%, at 1 year ($P < 0.05$), and this suppressive effect was maintained until 5 years (Fig. 3d).

Discussion

In this study, we observed longitudinal changes in BMD in elderly PHPT patients who underwent PTX. Several previous studies have pointed out the possibility of a high morbidity rate for elderly patients and prolonged postoperative hypocalcemia (so-called hungry bone syndrome) [12]. However, in this study, we found that surgery was performed with low morbidity, and that serum calcium levels of all patients remained above 2.1 mmol/l throughout the follow-up period, although eight patients required additional supplementation with calcium or active vitamin D_3 or both.

In the lumbar spine, PTX resulted in a significant increase in BMD. We have already reported this effect in a 1-year follow up study [7], and here we report its continuity for at least 5 years. Recent general recommendations suggest PTX for those with T-scores at the lumbar spine or hip below –2.5, which is currently defined by the World Health Organization (WHO) as osteoporosis [13]. In our study, baseline LSBMD and lumbar T-scores were much lower than in previous reports [4]. The reason for this decrease may be that our subjects were older, and most of them were postmenopausal women who are more susceptible to primary osteoporosis, which affects mainly cancellous bone, than younger subjects. The lumbar T-scores in this study improved from below –2.5 to above –1.5, in which range vertebral fractures are less likely to occur. However, in the distal third of the radius, which contains mainly cortical bone, PTX did not provide a positive effect, with T-scores remaining below –2.5 throughout the entire period, or even showing a slight decrease. The total femur, which contains

mainly cancellous bone, showed a remarkable gain in BMD and T-scores comparable to the spine after PTX, but the change at 5 years after PTX was not statistically significant compared to the preoperative value, probably because of the small number of cases.

It has been a source of controversy whether PTX provides successful BMD increases only in cancellous bone or in both cancellous and cortical bone. Although cortical bone is more vulnerable to the catabolic effects of PTH, Silverberg et al. have reported that BMD undergoes rapid and sustained increases at cancellous bone sites after PTX, whereas smaller changes take place at cortical bone sites [4]. They attempted to explain this paradoxical phenomenon by hypothesizing that PTX restores normal pulsatility to PTH secretion, which has an anabolic effect on cancellous bone.

Recently, Nomura et al. reported that PTX led to significant increases in BMD in Japanese PHPT patients over 6 years, not only in the lumbar spine, but also in distal parts of the radial bone [14]. As an explanation for this result, which is discrepant with the results of Silverberg et al., they mentioned the possibility of racial differences or their selection of patients with relatively higher PTH levels. In our study, as already mentioned, radial BMD showed no increase after PTX, a result compatible with that of Silverberg et al. It should be noted, however, that the baseline Z-scores of radial BMD of the patients described by Nomura et al. (–3.33 ± 0.27) were significantly lower than those of our patients (–0.85 ± 0.96; see Table 1), and their Z-scores 6 years after PTX, which they say increased significantly, were still lower than our baseline level. The baseline level of radial BMD may have a large effect on the degree of BMD increase, as the Nomura group themselves reported in another paper that BMD changes after PTX could be predicted from preoperative Z-scores of radial BMD; the increases in BMD were significantly higher in groups with Z-scores below –2 than in groups with Z-scores of –2 or more [15]. One of the reasons for the relatively small decrease in the baseline radial Z-scores in our patients may be that our study was conducted using an older population. In most elderly women more than 10 years after menopause, loss of cortical bone occurs more dominantly than loss of cancellous bone, which, in turn, may result in a relatively mild attenuation of the Z-scores of radial or femoral BMD in older PHPT patients, and thus obscure the amelioration in BMD of those sites after PTX. Some studies involving postmenopausal women are supportive of this hypothesis. Hagstrom et al. showed in another report that PTX significantly increased BMD in the lumbar spines of all postmenopausal women enrolled in the study, but femoral neck BMD increased only in the younger half of all subjects [16]. However, even after considering these points, the absolute FBMD in our patients, whose average baseline T-score was already above –2.5, are high. This, together with the low number of patients, may have resulted in the lack of a significant increase in T-scores at this site.

As for fracture risk, some studies have already shown that PHPT patients have a higher risk of fractures than control patients [1]. However, it remains controversial whether PTX can decrease the fracture risk in PHPT patients. Vestergaard et al. reported that the increased risk of fractures observed in the vertebrae, lower leg, ankle, and nondistal parts of the forearm was all normalized following PTX [17]. They further showed in a subsequent report that PTX reduces the risk of hip and upper arm fractures [18]. VanderWalde et al. showed in another report that PTX is associated with a significant decrease in the risk of fractures in the hip and upper extremities, and a significant increase in the fracture-free survival rate of PHPT patients regardless of age (above or below 50 years) [19]. Unfortunately, neither study could find a decreased fracture rate in the spine, but this is partially because these studies were population-based, retrospective studies, so that many asymptomatic spine fractures may have been overlooked.

It has been controversial whether PTX should be recommended for all patients with PHPT, including asymptomatic patients. Silverberg et al. reported that most asymptomatic PHPT patients who did not undergo surgery did not experience disease progression, and that there were no remarkable changes in serum calcium, PTH level, or fracture risk [5]. In the reports of Vestergaard and VanderWalde, baseline plasma calcium levels in the no-surgery group were 2.74 and 2.77 mmol/l, respectively, both higher than the levels reported by Silverberg (2.62 mmol/l). These results support the validity of the guidelines of the NIH Consensus Conference, which recommend PTX for patients whose calcium level is more than 0.3 mmol/l above the reference ranges. Further studies are needed to clarify the correlation between the severity of disease and the effectiveness of PTX.

In this study, we observed no newly suffered fractures because of the small number of cases. However, based on the previous reports that PTX decreased the risk of fractures even in the patients aged 50 years and older, and the fact that both lumbar and femoral T-scores reached levels above –1.5 in our study, it seems likely that PTX can effectively prevent fractures in those sites even in elderly patients, at least those with higher prior serum calcium levels.

Bone turnover in PHPT demonstrates a typically high pattern accompanied by high levels of bone formation and resorption markers [20]. PTX treatment of elderly PHPT patients inhibits bone formation and resorption from the point of view of those markers for at least 3 years. Although the differences in IOC and NTx levels after 5 years were not statistically significant compared with baseline values, they remained almost at the same levels for 3 years. Collection of data from a larger sample will confirm the efficacy of PTX in the elderly.

There are some limitations in our study. First, as already mentioned, the number of subjects was relatively small, especially in terms of the femoral and radial BMD data, which might have an effect on the finding of no significant difference over time in FBMD. Furthermore, our study is not a prospective study and involves no control subjects. A large, randomized control trial investigating fracture risk is needed to elucidate the susceptibility of various bone sites to PTX in elderly PHPT patients.

In conclusion, for the management of elderly PHPT patients, PTX is preferable in terms of the improvement of BMD, at least in the lumbar spine, and it is expected that it has a protective effect on this site from compression fractures. However, careful consideration should be given to whether PTX should be performed in elderly patients with low BMD exclusively in cortical bone.

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