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Attenuation of Postmenopausal Bone Loss in Patients with Transient Hypoparathyroidism After Total Thyroidectomy

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Abstract

Background Increased bone mineral density (BMD) has been reported in patients with postsurgical permanent hypoparathyroidism. Hypoparathyroidism may attenuate the high-turnover bone loss in postmenopausal women. We reported previously that patients who had transient hypoparathyroidism postoperatively were at subclinical hypoparathyroid (hP) status even 5 years after surgery. We hypothesized that patients with transient hypoparathyroidism (ThP) may have altered BMD.

Methods A total of 140 women who underwent total thyroidectomy had BMD measurements of the lumbar spine, femoral neck, and radius 3 years after surgery. At surgery, 99 patients were ≥50 years and 41 were <50 years. They were divided into three groups according to their postoperative parathyroid function: There were 80 patients in the no hP (NhP) group, 54 in the ThP group, and 6 in the permanent hP (PhP) group.

Results Among the 99 patients aged ≥50 years, 36 ThP patients had median *Z* scores of the BMD in all three areas (lumbar spine, femoral neck, radius) that were significantly higher (by 1.083, 0.533, and 1.047, respectively) than those in the 60 NhP patients aged ≥50 years. The BMDs in the three PhP patients ≥50 years were higher than those in the NhP and ThP patients, but the difference did not reach significance except for in the femoral neck. Multivariate logistic regression analyses showed that *Z* scores > 0 were significantly associated only with the presence of ThP postoperatively. In the patients <50 years, the BMD values were not significantly different among the three groups except at the radius in PhP patients, which was significantly lower than those of the other patients.

Conclusions We found that ThP was associated with increased BMD in postmenopausal women. This may be due to attenuation of the high-turnover bone loss in postmenopausal women.

Introduction

Hypoparathyroidism is one of the major complications of total thyroidectomy, and its adverse symptoms are of concern [1, 2]. Individuals with permanent hypoparathyroidism were found to have higher bone mineral density (BMD) than age- and sex-matched controls [3, 4], although there are conflicting reports on this issue [5]. Touliatos et al. [6] reported that eight patients with postsurgical hypoparathyroidism had BMD values above the normal mean, although the patients had several risk factors for osteoporosis, including hypogonadism, an inactive lifestyle, and others.

Parathyroid hormone (PTH) is a key hormone involved in the maintenance of serum calcium levels and systematic regulation of bone resorption. Fujiyama et al. studied the BMD in 33 postmenopausal patients who underwent total thyroidectomy. They reported that postoperatively the age-matched BMD values were clearly higher and the incidence of spinal deformity was significantly lower in the 13 patients with postsurgical hypoparathyroidism than in the 20 patients with normal parathyroid function [7]. They suggested that the hypoparathyroid condition provided protection against postmenopausal high-turnover bone loss.

As endocrine surgeons, we usually try to preserve the parathyroid glands in situ with their vascular supplies. If

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Table 1 Clinical features of the 140 thyroid cancer patients who underwent total thyroidectomy

Characteristic	NhP group	ThP group	PhP group	*p* value
No. of patients	80	54	6	
Age (years), mean and range	56.4 (21–82)	53.2 (29–75)	51.5 (29–69)	NS
Cancer histopathology				
Papillary	78	54	6	
Medullary	1	0	0	
Follicular	1	0	0	
Operation				
TT + CND + MND	37	24	5	
TT + CND	40	29	1	
TT	3	1	0	
Parathyroid glands				
Preserved	1.91 (0–4)	1.80 (1–3)	0.83 (0–1)	<0.05*
Transplanted	1.71 (0–3)	1.98 (0–4)	1.67 (0–3)	NS
Vitamin D				
Alfacalcidol (μg/day)	None	0.97 (0.5–2)	1.10 (0.5–2)	
Duration (days)	–	94.3 (16–316)	1198 (567–1836)	<0.005
Total dose (μg)	–	93.3 (8–316)	1,326 (567–1,836)	<0.005
Calcium				
Calcium lactate (g/day)	None	5.3 (4–8)	4.8 (4–8)	
Duration (days)	–	18 (1–90)	20 (12–23)	NS
Total dose (g)	–	105.3 (20–368)	88 (40–160)	NS
TSH score[a]	2.4 (1.6–3.5)	2.4 (1.9–3.5)	2.5 (2.1–2.7)	NS

Unless otherwise stated, the values are the number of patients or mean (ranges)

NhP no hypoparathyroidism, *ThP* transient hypoparathyroidism, *PhP* permanent hypoparathyroidism, *TT* total thyroidectomy, *CND* central node dissection, *MND* modified neck dissection, *TSH* thyroid-stimulating hormone

* $p = 0.0013$ (NhP vs. PhP); $p = 0.012$ (ThP vs. PhP)

[a] According to Cooper et al. [9] and Jonklaas et al. [10]

successful, parathyroid function is maintained. If the parathyroid glands are resected, they are minced or sliced and transplanted into muscular pockets. Following these procedures, serum calcium and PTH levels usually recover to the normal range after transient hypoparathyroid status for several weeks after surgery. However, we found and reported that patients who had parathyroid autotransplantation without in situ preservation and who showed recovery in their serum calcium and PTH levels had significantly lower serum calcium and intact PTH (iPTH) levels compared to patients with parathyroid glands preserved in situ, even 5 years after surgery [8]. This status may be called subclinical hypoparathyroidism. Patients with postoperative transient hypoparathyroidism may also have this status, and it may persist for a long period. We hypothesized that postoperative transient hypoparathyroidism, or subclinical hypoparathyroidism, may also attenuate postmenopausal high-turnover bone loss, thereby reducing the decrease in BMD in postmenopausal patients.

Patients and methods

A total of 140 women with a mean age of 56.4 years (range 21–82 years) underwent total thyroidectomy for thyroid cancer at Kuma Hospital between January 2005 and December 2009. BMD was measured 3 years after the surgery in each patient (Table 1). At the time of surgery, 99 patients were ≥50 years of age, and the remaining 41 were <50 years. The thyroid cancers included 138 papillary carcinomas, 1 follicular carcinoma, and 1 medullary carcinoma. Total thyroidectomy with central node dissection was performed in all but four patients who underwent total thyroidectomy only. In all, 66 patients also underwent modified neck dissection. All of the surgery was performed by skilled endocrine surgeons. We tried to preserve parathyroid glands in situ with their blood supply. However, if they were resected or devascularized, they were minced and autotransplanted into the sternocleidomastoid muscle. The numbers of preserved and transplanted parathyroid glands are shown in Table 1.

According to the postoperative parathyroid function, the patients were divided into three groups. The no hypoparathyroid (NhP) group consisted of 80 patients whose serum iPTH level was >10 pg/ml (normal 15–70 pg/ml) 1 day after surgery and did not require vitamin D. The transient hypoparathyroid (ThP) group included 54 patients whose serum iPTH level was <10 pg/ml 1 day after surgery, and their hypoparathyroid status recovered within 1 year. The permanent hypoparathyroid (PhP) group consisted of 6 patients whose iPTH level was <10 pg/ml 1 day after surgery, and their hypoparathyroid status persisted for more than 1 year (Table 1).

The mean ages of the three groups were not significantly different. The patients in the ThP and PhP groups were prescribed alfacalcidol and calcium lactate. The doses and durations of the prescriptions are shown in Table 1. The ThP patients had been administered alfacalcidol (mean dose 0.97 μg/day; total dose 93 μg) for a mean period of 94 days and calcium lactate (mean dose 5.3 g/day; total dose 105 g) for a mean period of 18 days. The extent of suppression by the thyroid-stimulating hormone (TSH) might influence the patients' BMDs. A mean TSH score to evaluate the extent of TSH suppression was calculated for each patient by averaging all available TSH determinations—1, undetectable TSH; 2, subnormal TSH; 3, normal TSH; 4, elevated TSH—as described by Cooper et al. [9] and Jonklaas et al. [10]. These scores were not significantly different among the NhP, ThP, and PhP groups (2.4, 2.4, and 2.5, respectively) (Table 1). These scores indicated that TSH suppression among the patients was mild on average.

The BMD values were measured in the lumbar spine (L2–4), femoral neck, and radius (33 % distal end of the radius) using dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy; GE Healthcare, Milwaukee, WI, USA) 3 years ± 3 months after the individual patient's surgery. The BMD results were compared with those of age-matched controls and are shown as the Z score of the BMD [11]. The significance of differences in the variables among the groups in Tables 1 and 2 was calculated using Student's t test and the χ^2 test. The significance of differences in BMD values was calculated using the Mann–Whitney test. Multivariate logistic regression analyses for factors related to Z scores > 0 were performed. All statistical tests were two-sided, with the level of significance established at $p < 0.05$. Statistical analyses were performed using StatFlex Version 6.0 software (Artech Co., Ltd., Osaka, Japan).

Results

Figure 1 shows the BMD results obtained by DXA. The Z scores of BMD of the lumbar spine and radius, but not that of the femoral neck, were significantly higher in the ThP group than in the NhP group: lumbar spine 1.262 versus 0.511 and radius 0.414 versus −0.096 (for median values) ($p < 0.05$); femoral neck 0.775 versus 0.400 (for median values) (NS). The Z scores of BMD at these sites were higher in the PhP group than the NhP group, but the difference was not significant.

We also divided the 140 patients by their age at surgery. Patients who are ≥50 years correspond to postmenopausal women, and those <50 years old correspond to premenopausal women. According to a report on age at natural menopause in Japanese women, the average age of menopause was 50.5 years [12]. The numbers of patients ≥50 years in our series were 60 NhP patients, 36 ThP patients, and 3 PhP patients. In this subgroup of 99 patients ≥50 years at surgery, the Z scores of BMD of the lumbar spine, femoral neck, and radius were significantly higher in the ThP patients than in the NhP patients: lumbar spine

Table 2 Mean serum calcium levels before and 3 years (±3 months) after surgery, by the postoperative parathyroid function groups

Group	No.	Before surgery	After surgery	p value
NhP	80	9.17 ± 0.451	9.20 ± 0.374	NS
ThP	54	9.20 ± 0.409	8.85 ± 0.545	<0.05
PhP	6	8.98 ± 0.349	9.07 ± 0.423	NS

Calcium data are shown as mean ± SD (mg/dl). Patients in the PhP group were on alfacalcidol 3 years after surgery

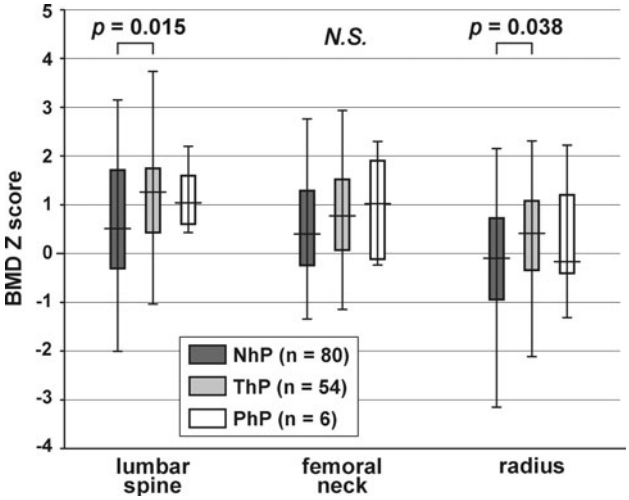

Fig. 1 Bone mineral density (BMD) values obtained by dual-energy X-ray absorptiometry (DXA) in thyroid cancer patients 3 years after surgery. The Z scores of BMD of the lumbar spine and radius were significantly higher in the ThP group than in the NhP group. *Whiskers* represent extreme values; *edges of boxes* represent the quartiles; *horizontal bold lines* represent the median value. The p values are derived from Mann–Whitney tests. *NhP* no hypoparathyroidism, *ThP* transient hypoparathyroidism, *PhP* permanent hypoparathyroidism

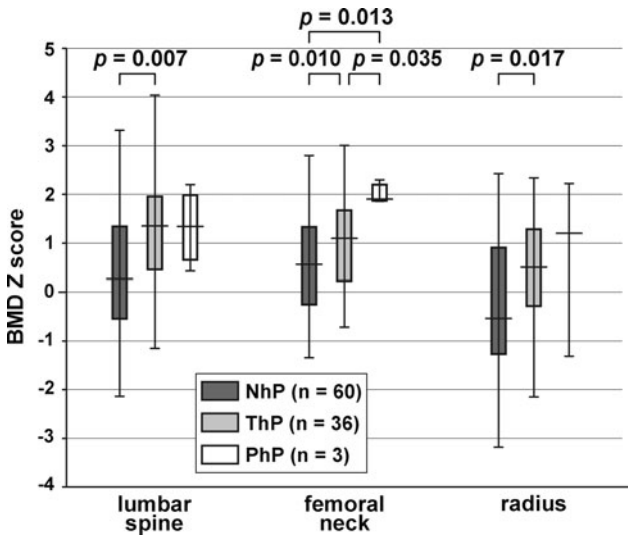

Fig. 2 BMD values obtained by DXA in female patients ≥50 years of age at surgery. *Z* scores of the BMD of the lumbar spine, femoral neck, and radius were significantly higher in the ThP group than in the NhP group. *Z* scores of BMD in the PhP group were higher than those in other groups. The differences did not reach significance except for the femoral neck because of the small number of patients in this group. *Whiskers* represent extreme values; *edges of boxes* represent the quartiles; *horizontal bold lines* represent the median value. For the PhP group the median, largest, and smallest values are shown because the group had only three patients. The *p* values are derived from Mann–Whitney tests

1.350 versus 0.268, $p = 0.007$; femoral neck 1.096 versus 0.563, $p = 0.010$; radius 0.508 versus −0.539, $p = 0.017$ for median values). The *Z* scores of BMD in the PhP patients (lumbar spine 1.343; femoral neck 1.903; radius 1.200 for median values) were higher than those in the NhP and ThP patients, but the differences did not reach significance except for the femoral neck (because there were only three patients in this group) (Fig. 2; Table 3).

In contrast, in the subgroup of 41 patients <50 years at surgery, the *Z* scores of BMD of the lumbar spine, femoral neck, and radius were not significantly different among the three groups except for the radius scores in the PhP patients, which were significantly lower than those of the NhP patients (Fig. 3; Table 3).

The serum calcium levels at the time of the DXA scan did not differ significantly from their preoperative levels in the NhP and PhP groups. In the ThP group with postoperative transient hypoparathyroidism, the serum calcium levels at the time of the DXA scan were within normal limits, but they were significantly lower than their preoperative levels (8.85 vs. 9.20 mg/dl, $p < 0.05$; normal range: 8.2–10.2 mg/dl), suggesting that these patients had subclinical hypoparathyroidism 3 years after their surgeries (Table 2).

As described above, the present data revealed significantly higher BMDs in the ThP group than in the NhP group among patients ≥50 years. Multivariate logistic regression analyses in these patients showed that *Z* scores > 0 was significantly associated only with the presence of transient hypoparathyroidism postoperatively and not with the total dose of vitamin D (Table 4).

Table 3 *Z* scores of BMD in the lumbar spine, femoral neck, and radius according to age at surgery and parathyroid status group

Bone site	*Z* score of BMD			*p* value
	Group	Median	IQR 25th–75th	
Age ≥50 years				
Lumbar spine	NhP	0.268	−0.545 to 1.339	–
	ThP	1.350	0.461–1.953	0.007
	PhP	1.343	0.430/2.200[a]	NS
Femoral neck	NhP	0.563	−0.251 to 1.328	–
	ThP	1.096	0.229–1.670	0.010
	PhP	1.903	1.859/2.300[a]	0.013
Radius	NhP	−0.539	−1.267 to 0.906	–
	ThP	0.508	−0.283 to 1.281	0.017
	PhP	1.200	−1.312/2.225[a]	NS
Age <50 years				
Lumbar spine	NhP	1.153	0.303–2.100	–
	ThP	1.146	0.432–1.543	NS
	PhP	0.742	0.603/1.595[a]	NS
Femoral neck	NhP	0.364	−0.243 to 0.992	–
	ThP	0.210	−0.616 to 0.661	NS
	PhP	−0.115	−0.238/0.187[a]	NS
Radius	NhP	0.313	0.046–0.584	–
	ThP	0.150	−0.340 to 0.806	NS
	PhP	−0.365	−0.404/0.035[a]	0.040

The *p* values indicate significance compared with the values for the NhP group

NhP no hypoparathyroidism, *ThP* transient hypoparathyroidism, *PhP* permanent hypoparathyroidism, *IQR* interquartile range

[a] The smallest/largest values are shown because the PhP group consisted of only three patients

Discussion

Several investigators have shown that estrogen deficiency following menopause results in rapid bone loss in postmenopausal women [13, 14]. This is a major cause of osteoporosis, carrying an increased risk of bone fracture. In 1970, Hossain and Smith [15] studied the metacarpal cortical thickness in women with hypoparathyroidism and hyperparathyroidism and reported that the hypoparathyroid postmenopausal women's values were above the normal mean for their age. They suggested that age-related osteoporosis was hormonal in origin. Seeman et al. [3] reported that 20 patients with postsurgical hypoparathyroidism had

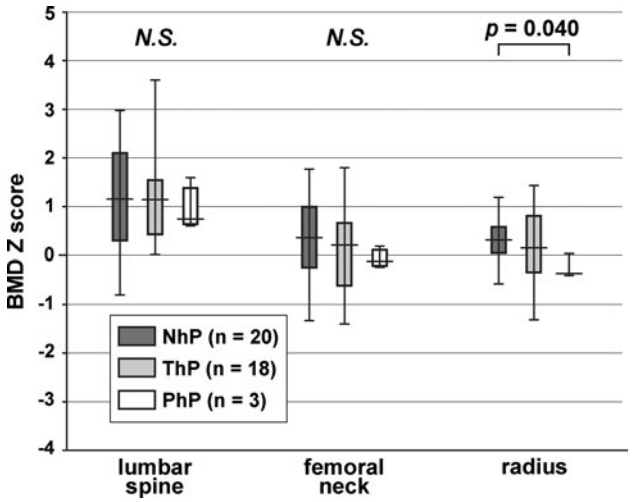

Fig. 3 BMD values obtained by DXA in female patients <50 years of age at surgery. *Z* scores of BMD of the lumbar spine, femoral neck, and radius were not significantly different among the groups except for the radius in the PhP group, which was significantly lower than that in the NhP group. *Whiskers* represent extreme values; *edges of boxes* represent the quartiles; *horizontal bold lines* represent the median value. For the PhP group the median, largest, and smallest values are shown because the group had only three patients. The *p* values are derived from Mann–Whitney tests

Table 4 Multivariate logistic regression analysis for *Z* score > 0 in patients age ≥50 years with no or transient hypoparathyroid function postoperatively

Bone site	*p* value	OR	95 % CI
Lumbar spine			
Total VD dose	0.2665	0.996	0.989–1.003
ThP	0.0232	3.996	1.208–13.22
Femoral neck			
Total VD dose	0.2621	0.996	0.988–1.003
ThP	0.0224	5.113	1.260–20.76
Radius			
Total VD dose	0.5093	0.998	0.993–1.004
ThP	0.0049	4.075	1.532–10.84

VD vitamin D (alfacalcidol), *OR* odds ratio, *CI* confidence interval

higher BMD values at the lumbar spine and radius than normal subjects. Eight patients with postsurgical hypoparathyroidism studied by Touliatos et al. [6] that had BMD values above the normal mean, even though they had one to four risk factors for osteoporosis. Abugassa et al. [4] studied 19 patients with postsurgical hypoparathyroidism and found that their bone mass was 10–32 % greater than that of normal controls. All of their patients with postsurgical hypoparathyroidism were treated with vitamin D with or without a calcium preparation for a long period. The authors suggested that reduced PTH production, vitamin D treatment, and calcium supplementation might have contributed to the increased bone mass in these patients [4]. None of the studies described above specifically mentioned the patients' age or menopausal status.

Fujiyama et al. [7] studied BMD in 33 postmenopausal patients who underwent total thyroidectomy for thyroid cancer. They reported that the age-matched BMD values were clearly higher in the 13 patients with postsurgical hypoparathyroidism than in the 20 patients with normal postoperative parathyroid function. This phenomenon was more evident in patients during the early postmenopausal period (within 5 years after menopause). Those authors also reported that the incidence of spinal deformity was significantly lower in the postsurgical hypoparathyroid patients than in those with normal parathyroid function. They suggested that the hypoparathyroid condition provides protection against age-related bone loss by attenuating the high-turnover bone loss following menopause [7].

Patients with differentiated thyroid cancer are usually offered TSH suppressive therapy of varying degrees, depending on the risk of cancer recurrence. Biondi and Cooper [16] reviewed the benefits of TSH suppressive therapy and the risks of its adverse effects, and they proposed osteoporosis as one of the possible adverse effects. They summarized that TSH suppression did not affect BMD in men or in premenopausal women, whereas postmenopausal patients were at risk of bone loss [16]. In another report, TSH suppressive therapy was associated with significant bone loss in postmenopausal women but not in premenopausal women [17]. In Japanese women ≥50 years of age, TSH suppressive therapy had adverse effects on BMD according to Sugitani and Fujimoto [18], but conflicting data were reported by Fujiyama et al. [7] and Schneider et al. [19]. They did not find BMD loss in association with TSH suppressive therapy. In the present study, the extent of TSH suppression was mild as suggested by the mean TSH score (2.4–2.5), which did not significantly differ among the three groups. Thus, the effect of TSH suppressive therapy on the present study population was negligible.

The present data demonstrate that the postmenopausal patients who had postsurgical transient hypoparathyroidism had higher BMD values than those with normal parathyroid function postoperatively. Patients with transient hypoparathyroidism had serum calcium levels 3 years after surgery that were within normal ranges but were significantly lower than their preoperative values, indicating that these patients maintained a subclinical hypothyroid status for 3 years. The duration of alfacalcidol treatment was short and the total dose small. The multivariate logistic analyses showed that *Z* scores > 0 was significantly associated only with the presence of transient hypoparathyroidism postoperatively and not with the total dose of vitamin D. Therefore, high BMDs in ThP patients may be

due to an attenuation of high-turnover bone loss after menopause. Permanent hypoparathyroidism should be avoided because it necessitates lifelong vitamin D treatment. Also, it is associated with hypercalciuria, calcification of the kidneys and basal ganglia, and decreased renal function. However, to the best of our knowledge, no adverse results of transient hypoparathyroidism or subclinical hypoparathyroidism have been reported.

Conclusions

As endocrine surgeons, we usually try to preserve parathyroid glands in situ. However, the present findings may indicate that leaving postmenopausal patients in a ThP status postoperatively may be beneficial for the patients in terms of avoiding or attenuating postmenopausal bone loss. Doing so should be technically easy. We can remove all parathyroid glands during total thyroidectomy and transplant the resected parathyroid glands into muscle. Further studies are needed to clarify whether this procedure is beneficial for postmenopausal patients who undergo total thyroidectomy.

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Conflict of interest None.

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