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Effects of denosumab as compared with parathyroidectomy regarding calcium, renal, and bone involvement in osteoporotic patients with primary hyperparathyroidism

Daichi Miyaoka, Yasuo Imanishi, Eiko Kato, Norikazu Toi, Yuki Nagata, Masafumi Kurajoh, Shinsuke Yamada, Masaaki Inaba, Masanori Emoto

Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine

Address all correspondence to: Daichi Miyaoka, MD, PhD

Department of Metabolism, Endocrinology and Molecular Medicine

Osaka City University Graduate School of Medicine

1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan

Tel: +81-6-6645-3806, Fax: +81-6-6645-3808,

Email: d.miyaoka0914@gmail.com

Abstract

Purpose: To evaluate the effects of denosumab (Dmb) on calcium, renal, and bone involvement in osteoporotic patients with primary hyperparathyroidism (PHPT) and compare with those who underwent a parathyroidectomy (PTX) procedure.

Methods: This retrospective, longitudinal study included patients treated with Dmb (60 mg) once every 6 months (n=19) and those who successfully underwent a PTX procedure (n=19) Corrected calcium (cCa), eGFR, bone mineral density (BMD) in the lumbar spine (LS), total hip (TH), and

femoral neck (FN) and LS-trabecular bone score (TBS) changes at 1 year after beginning Dmb or undergoing PTX were measured.

Result: Dmb group had older age, and showed milder disease activity and lower eGFR as compared to PTX group. In PTX group, cCa and eGFR were significantly decreased following surgery, while those were stable in Dmb group. There were significant increases in LS, TH, and FN-BMD in both Dmb (LS: 6.0±0.8%, TH: 3.7±1.0%, FN: 4.3±1.5%) and PTX (LS: 11.2±1.5%, TH: 7.5±1.5%, FN: 7.9±2.1%) groups. In Dmb group, LS-TBS was significantly improved by 3.0±1.0%, while TBS change in PTX group approached significance (2.8±1.5%). Percent change in TH-BMD was significantly correlated with baseline tartrate-resistant acid phosphatase-5b (TRACP-5b) in both groups.

Conclusion: Dmb treatment not only increased BMD, dependent on bone turnover status, the same as PTX, but also improved LS-TBS. Additionally, it did not decrease the level of eGFR, whereas PTX did. These results suggest that Dmb treatment help in the clinical management of osteoporotic patients with PHPT who do not undergo surgery as alternative to PTX.

Keywords

primary hyperparathyroidism, denosumab, parathyroidectomy, osteoporosis, bone mineral density, trabecular bone score

Declarations

Funding

No funding was received.

Conflicts of interest

M.I. received grant support and lecture fees from Daiichi Sankyo Co., Ltd. Y.I. and E.M. received lecture fees from Daiichi Sankyo Co., Ltd. D.M., E.K., N.T., Y.N., M.K., and S.Y. have no conflicts of interest to report.

Ethics approval

The study protocol was approved by the institutional ethics committee of Osaka City University Graduate School of Medicine (approval No. 2019-072) and conducted in accordance with the principles of the Declaration of Helsinki.

Authors' contributions

Y.I., and M.I. contributed to the concept and design of the study. D.M. contributed to the acquisition, analysis, and interpretation of data. E.K., N.T., Y.N., M.K., S.Y., and M.E. contributed to the acquisition of data. D.M. was responsible for the integrity of the data analysis. D.M. and Y.I. drafted and revised the manuscript. All authors have approved the final version of the manuscript.

Introduction

Primary hyperparathyroidism (PHPT), the third most frequent endocrine disorder, increases with age and is often diagnosed in patients without clinical symptoms [1]. A parathyroidectomy (PTX) procedure is the only definitive treatment, even for asymptomatic patients, and reduces the risk of kidney stones and fractures [2], though a progressive age-related decline in the rate of PTX procedures after the age of 70 years has been noted [3]. As for PHPT patients who cannot or refuse to undergo surgery, calcium, renal, and bone-protective strategies as an alternative to PTX are available, yet remain controversial.

The 2014 International Guidelines for the Management of Asymptomatic PHPT [2] recommended increased research over the ensuing 5 years, including analytical analyses such as trabecular bone score (TBS) for fracture risk and pharmacological approaches used to treat affected patients. TBS is an indirect index of trabecular bone microarchitecture used to evaluate pixel gray-level variations in dual energy x-ray absorptiometry (DXA) images of the lumbar spine (LS) [4] and has been shown to be a novel predictor of risk of major osteoporotic fracture independent of bone mineral density (BMD) [5]. Also, in previous studies of patients with PHPT, TBS values were significantly lower than those of matched controls and better predicted vertebral fracture at any site than BMD [6, 7], suggesting that TBS is a useful clinical tool for assessment of skeletal involvement in these patients. Bisphosphonates, especially alendronate, have been shown to cause a reduction in bone turnover markers (BTMs) and increase in BMD, and their administration is currently recommended as the main medical option for treating osteoporosis in PHPT [8]. However, careful consideration is needed to use any bisphosphonate in patients with renal impairment because of nephrotoxicity and accumulation [9]. Also, bisphosphonates were recently reported to be associated with increased fracture risk in PHPT patients after stratification based on baseline BMD status [10], suggesting that bisphosphonate-associated gains in BMD do not translate into a benefit with respect

to fracture risk.

Denosumab (Dmb), a fully human monoclonal antibody to RANKL, is an anti-resorptive agent approved for treatment of osteoporosis, and likely effective at reducing fracture risk and increasing BMD in postmenopausal women with renal impairment [11]. Although a recent study reported that Dmb was efficacious for increasing BMD in older women with PHPT [12], no investigation that compared the calcium-, renal-, and bone-protective effects of Dmb in PHPT patients with those of PTX has been published. Furthermore, though it was reported that Dmb significantly improved TBS independently of BMD in postmenopausal women [13], no known studies have explored the effects of Dmb on TBS in osteoporotic patients with PHPT.

The aims of this study were to compare the effects of Dmb with those of PTX on (1) calcium and renal involvement, as well as (2) BMD and LS-TBS, and (3) also determine the relationship of BTMs to changes in BMD and LS-TBS in osteoporotic patients with PHPT.

Methods

Study design and participants

Nineteen osteoporotic patients with PHPT who began Dmb treatment (60 mg, once every 6 months) in the period from March 2014 to March 2018 at Osaka City University Hospital were enrolled and followed for 12 months. Inclusion criteria were as follows: (1) meets biological diagnosis of PHPT based on whole PTH >38.7 pg/mL or inappropriately normal level in the presence of elevated corrected calcium (cCa >10.2 mg/dL), or elevated PTH level with normocalcemia and no cause of secondary hyperparathyroidism [14], (2) meets indications for surgery for bone involvement with a BMD T-score of -2.5 or lower for LS, TH, or FN shown in DXA imaging, at least 1 vertebral fracture, or currently receiving treatment for osteoporosis, (3) receiving Dmb treatment because of inability; non-conclusive pre-surgical localization (n=9) and high anesthesia risk (n=7), or refusal (n=3) to undergo surgery. Of the Dmb groups (n=19), four patients are normocalcemic PHPT, but all these patients had a pre 25OHD level above 20 ng/mL, and started daily supplementation with Ca at 610 mg, cholecalciferol at 400 IU, and Mg at 30 mg at least 1 month prior to initiation of Dmb treatment, resulting in no decrease of elevated PTH level.

In addition, PHPT patients who treated with PTX at our department between March 2016 and March 2018 were also enrolled (n=57). Following enrollment, 38 patients were excluded because of no BMD follow-up available (n=29), persistent hypercalcemia after PTX (n=1), familial PHPT (n=5), parathyroid cancer (n=1), and no skeletal indication for surgery (n=2). After all, this group included a total of 19 patients. The PTX groups, including two patients with normocalcemic PHPT, histopathologically confirmed as PHPT because of parathyroid adenoma and completed longitudinal follow-up examinations, including clinical, biochemical, and DXA assessments, before and 1 year after undergoing PTX.

The study protocol was approved by the institutional ethics committee of Osaka City

University Graduate School of Medicine (approval No. 2019-072) and conducted in accordance with the principles of the Declaration of Helsinki.

BMD and TBS measurements

BMD for LS, TH, or FN was assessed by DXA using the Hologic QDR 4500A DXA system (Hologic Inc., Marlborough, MA, USA) at the baseline and 12 months after beginning Dmb therapy or undergoing PTX. All TBS measurements obtained with the DXA system were analyzed using the TBS iNsight software package (Med-Imaps, Bordeaux, France). TBS values were obtained by directly reanalyzing a single acquired LS-DXA image. Regions showing degenerative changes and/or vertebral fractures were excluded from the LS-BMD and TBS calculations. Vertebral fractures were assessed using a semiquantitative method [15]. Participants were included if they had at least 2 measurable LS areas in the L1-4 region. TBS was determined in the same vertebrae and regions of measurement as those used for LS-BMD, with values calculated as the mean of individual measurements of the vertebrae.

Biochemical parameters

Serum and second-void urinary samples were collected in the morning after an overnight fast prior to Dmb administration or PTX. Ca, phosphate (Pi), creatinine (Cr), and alkaline phosphatase (ALP) in serum, as well as urinary Ca, Pi, and Cr levels were determined using an enzymatic method with a Hitachi 7450 autoanalyzer (Hitachi Co., Tokyo, Japan). When the serum albumin (Alb) level was <4.0 mg/dL, cCa level was calculated using the following equation:

cCa level = serum Ca level (mg/dL) + 4.0 - serum Alb level (g/dL)

Grading for the incidence of laboratory hypocalcaemia was classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Values for the percentage of tubular

reabsorption of Pi (%TRP) were calculated using the following equation:

$$\%TRP = 100 \times \{1 - (\text{urinary Pi} \times \text{serum Cr}) / (\text{urinary Cr} \times \text{serum Pi})\}$$

To assess renal function, eGFR was calculated using the following equation proposed by the Japanese Society of Nephrology [16], with the result for females multiplied by 0.742:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$$

Serum whole PTH (wPTH) was determined using an immunoradiometric assay (Scantibodies Laboratory, Inc., Santee, CA, USA). A 25-hydroxyvitamin D 125I RIA Kit (DiaSorin S. P. A, Saluggia, Italy) was utilized to determine serum 25OHD concentration. Radioimmunoassay findings were used to measure serum $1,25(OH)_2D$ (Immunodiagnostic Systems, England) and bone ALP (BAP) concentration was determined using an enzyme immunoassay (EIA) kit (Alkphase-B; Metra Biosystem, Mountain View, CA, USA). That latter assay is capable of detecting BAP ranging from 0.7-140 U/L, and the intra- and inter-assay coefficients of variation were 2.3% and 3.1%, respectively. Additionally, serum tartrate-resistant acid phosphatase-5b (TRACP-5b) was determined using a fragment-absorbed immunocapture enzymatic assay (Osteolinks TRACP-5b; DS Pharma Biomedical, Osaka, Japan), which is capable of detecting that in a range from 10-2800 mU/dL, with the intra- and inter-assay coefficients of variation reported to be 2.2% and 3.0%, respectively [17].

Statistical analysis

Values are expressed as number and percentage, mean ± standard deviation (SD), or median and interquartile range (IQR), as appropriate. Baseline characteristic values were analyzed with Student's *t*-test or Mann-Whitney *U*-test for continuous variables, and Fisher's exact probability test for categorical variables, as appropriate. Longitudinal changes in biochemical and DXA parameters were analyzed with an one-way repeated measures analysis of variance (ANOVA), followed by Dunnett's test and a paired *t*-test for each treatment group, as appropriate. Differences in longitudinal change

between treatment groups were analyzed with Student's *t*-test. Values for DXA parameters are presented as the mean ± standard error of the mean (SEM). Percent changes in DXA parameters from baseline to 12 months were calculated as absolute changes divided by baseline values. Pearson correlation coefficients were employed to examine correlations between baseline characteristics. Correlations between percent changes in DXA parameters and baseline characteristics were determined by use of Spearman's correlation coefficient. *P*-values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP software package, version 11.2.0 (SAS Institute, Cary, NC, USA).

Results

Participants and treatments

A comparison of baseline clinical profiles between the Dmb and PTX groups is shown in Table 1. No differences were found in regard to gender or BMI, while age was older and eGFR lower in the Dmb group. In addition, corrected and urinary Ca, and whole PTH, BAP, and TRACP-5b levels in serum were lower, and serum phosphorous and 25OHD levels were higher in Dmb as compared to PTX. Baseline LS, TH, FN-BMD, LS-TBS, and number of participants who had previously undergone anti-resorptive therapy were not different between the groups.

Three of the 38 participants had vertebral fractures, while all had at least 2 measurable LS areas in the L1-4 region (specifically, 36 and 2 had 4 and 3 measurable vertebrae, respectively). No significant correlation was found between baseline TBS and LS-BMD (r=0.270, p=0.101). Comparisons of other indications for surgery between the Dmb and PTX groups are also shown in Table 1. Calcium involvement and nephrolithiasis were significantly more frequent in the PTX group.

Dmb-induced short-term change in corrected calcium

The concentration of cCa rapidly decreased from day 1 in the Dmb group, with the minimum reached on day 7 (9.6±0.6 mg/dL; p=0.009 vs. baseline), before returning to the baseline level within 6 months (10.1±0.6 mg/dL; p=1.000). Although none of the Dmb group members exhibited symptomatic hypocalcemia during the study, Grade 2 hypocalcemia, defined as cCa <8.0 mg/dL, was observed in 1, which occurred during the initial course of treatment. The absolute decrease in cCa from baseline to day 7 ($\Delta cCa_{0\text{-}7day}$) after the first injection of Dmb was significantly lower in patients pretreated with bisphosphonates (-0.80±0.4 mg/dL; p=0.016) as compared to those without that therapy (-0.30±0.4 mg/dL). Furthermore, the $\Delta cCa_{0\text{-}7day}$ value was significantly lower after the second as compared to after the first injection (-0.11±0.5 mg/dL vs. -0.59±0.5 mg/dL; p=0.004).

Changes in biochemistry data 1 year after either Dmb or PTX

Table 2 shows the time course of changes in biochemistry data for cCa, wPTH, ALP, Pi, and eGFR at the baseline and after 12 months in both groups. In the PTX group, following surgery cCa was significantly decreased, while that remained stable after treatment in the Dmb group. Furthermore, serum PTH was significantly decreased in the PTX group, while that was mildly but significantly increased in the Dmb group. On the other hand, serum ALP level was significantly decreased in both groups, though the difference between them was not significant. As expected, the PTX patients showed significantly increased serum Pi, whereas that was significantly decreased in the Dmb group. In addition, eGFR was significantly decreased in the PTX group, while that in the Dmb group remained stable. Notably, urinary Ca was significantly decreased and %TRP significantly increased in both groups (data not shown).

Changes in BMD and LS-TBS after 1 year in both Dmb and PTX groups, and correlations to baseline BTMs

LS, TH, and FN-BMD were significantly increased in both the Dmb (LS: 6.0±0.8%, p <0.001; TH: 3.7±1.0%, p =0.002; FN: 4.3±1.5%, p=0.007) and PTX (LS: 11.2±1.5%, p <0.001; TH: 7.5±1.5%, p <0.001; FN: 7.9±2.1%, p=0.002) groups. While the PTX group had greater percent changes in LS and TH-BMD (p=0.005 and p=0.048), there was no difference in FN-BMD gain between the groups (p=0.172). In the Dmb group, LS-TBS was improved significantly by 3.0±1.0% (p=0.007), whereas there was approached significant change in the PTX group (2.8±1.5%; p=0.063) (Fig. 1).

Correlations between percent changes in DXA parameters after 12 months and BTMs are shown in Table 3. In the PTX group, percent changes in BMD at all sites were significantly correlated

with baseline TRACP-5b, but not with baseline ALP or BAP. On the other hand, in the Dmb group, only the percent change in TH-BMD was significantly correlated with all baseline BTMs. Notably, there was a strong positive correlation between percent change in TH-BMD and baseline TRACP-5b in each group (Dmb: ρ=0.705, p <0.001; (PTX: ρ=0.770, p <0.001).

Discussion

The present results revealed that osteoporotic patients with PHPT who received Dmb therapy because surgery was not possible or refused showed milder disease activity and a greater frequency of asymptomatic forms than those who underwent PTX. Furthermore, the Dmb group had a lower frequency of calcium involvement and nephrolithiasis as compared to the PTX group, while they also had older age and lower eGFR. Similar to the present study, it was previously reported that the clinical presentation of PHPT is greatly influenced by aging and PHPT patients >65 years old were characterized as having a lower frequency of renal stones, lower eGFR and predominance of bone involvement [18]. It was also reported that a slight decrease in renal function is associated with a more severe BMD decrease in PHPT cases [19]. Bone-protective management is important for these older and lower eGFR patients with PHPT as well as with primary osteoporosis.

In the patients who received Dmb, the present results showed a transient decrease in cCa, with the minimum reached on day 7 following the first injection and then remained stable at 1 year after treatment. On the other hand, those who underwent Dmb treatment showed a compensatory increase in serum wPTH, not only transiently following the first injection [20], but that was sustained at 1 year after treatment. The effects of this compensatory consequence on bone metabolism and tumor growth warrant further investigation. Also, Grade 2 hypocalcemia by CTCAE was only observed in 1 patient in whom preoperative localization was a concern but who refused surgery. The diagnosis was symptomatic PHPT with high bone turnover and renal insufficiency, which are independent risk factors for denosumab-induced reductions in cCa [17]. Similar to the recommendation in our previous report of osteoporotic patients, monitoring of serum Ca at approximately 1 week after the initial dose of Dmb is important in these PHPT patients.

In the PTX group, eGFR was significantly decreased, while it remained stable in the Dmb group. Although renal impairment, defined as eGFR less than 60 mL/min/1.73 m^2, has been regarded

as an indication for surgery in PHPT patients, a previous review concluded that there is no evidence to suggest that surgical treatment with a PTX procedure has a significant impact on renal function in those patients [21]. On the other hand, several recent studies have reported that PTX results in worsened renal function, especially in PHPT patients with eGFR greater than 60 mL/min/1.73 m^2 [22-24] with the present study showing similar results. However, the mechanism why the patients with no renal impairment had a renal function deteriorated after PTX is still unclear. In contrast, the pharmacokinetics and pharmacodynamics related to Dmb are not influenced by renal function [25], and we previously reported that Dmb therapy improved the glomerular filtration rate in osteoporotic patients with normal kidney function by lowering serum phosphate [26], suggesting its renoprotective effects even in PHPT patients.

After 1 year, Dmb treatment in PHPT patients significantly improved LS-BMD by 6.0%, as well as TH- and FN-BMD, while LS-TBS by 3.0%, with those latter improvements consistent with though greater than previously reported in postmenopausal women with osteoporosis (5.7% and 1.4%, respectively) [13]. In addition, other prior reports including ours showed greater improvement in TBS with anabolic therapy such as teriparatide as compared with a bisphosphonate [27, 28]. The potential mechanism by which Dmb, characterized as an anti-resorptive agent, causes improvement in TBS might be explained by a steady contribution of modeling-based bone formation [29]. Together with these previous findings, the present results regarding TBS support the concept that this score provides distinct information related to bone quality independent of BMD, and can be used as an additional tool in routine clinical practice for assessing the effect of treatment on skeletal involvement in PHPT patients, while they also indicate that denosumab-associated gains in LS-TBS may translate into reduced fracture risk. In patients who underwent a PTX procedure, TBS changes were close to significance. Similarly, other recent studies of PHPT patients reported no significant changes in TBS following PTX [30-32]. The present results, including greater percent changes in LS and TH-BMD in

the PTX group as compared to the Dmb group, suggest that magnitudes of gains in BMD rather than TBS reflect a large portion of the efficacy of PTX, with a strong association with reduced fracture risk.

Finally, we found that 1-year changes in TH-BMD were correlated with baseline TRACP-5b, after separate analysis of the Dmb and PTX groups. Together with the previous finding that circulating soluble RANKL is elevated in patients with mild PHPT, and a positive correlation with markers of bone resorption and rates of bone loss in the TH area [33], the present results support the idea that baseline TRACP-5b is the most useful clinical marker for predicting the effect of treatment with Dmb, as gains in TH-BMD explain a considerable proportion of the fracture risk reduction observed with Dmb therapy [34]. Also, measurement of baseline TRACP-5b before undergoing PTX would be useful to predict changes in TH-BMD following that procedure, as amino-terminal procollagen propeptide of type I collagen (P1NP) and cross-linked C-terminal telopeptide of type I collagen (βCTX) levels were shown to be potently related to LS-BMD changes in 1-year follow-up examinations [35].

This study has several limitations: First, the retrospective design and non-precise matching of individuals in the Dmb and PTX groups may have resulted in selection bias. Although the Dmb group patients showed milder disease activity, that is related to the real-world setting of the study, suggesting that the results are important for daily clinical practice. Second, the small sample size may have reduced the statistical power and thereby concealed possible relationships. Third, the follow-up period was limited to 1 year, thus long-term changes in calcium, and renal and bone involvement remain to be determined. Forth, we did not measure the distal third of the radius BMD. Finally, we examined BMD and TBS changes as bone-protective effects of treatment. A future study to elucidate the treatment effects of both Dmb and PTX on subsequent fracture risk reduction is necessary.

In summary, this is the first study to compare bone-protective and renal effects of Dmb therapy in osteoporotic patients with PHPT as compared to those who underwent a PTX procedure.

Taking into account all the limitations mentioned above, Dmb was found to not only increase BMD dependent on bone turnover status, the same as PTX, but also improved LS-TBS, which is beneficial to prevent fractures. In addition, the level of eGFR was not decreased following Dmb treatment, whereas that did occur in patients who underwent PTX. We concluded that Dmb therapy help in the clinical management of osteoporotic patients with PHPT who are unable to undergo or refuse surgery as alternative to PTX.

Table 1. Baseline clinical profiles and other indications for surgery in Dmg and PTX groups

Characteristic	Dmb (n=19)	PTX (n=19)	P value
Gender, female/male	17/2	15/4	0.660
Age, years	71.8±7.1	63.2±10.4	0.005
BMI, kg/m^2	22.6±3.2	23.3±4.3	0.542
eGFR, $mL/min/1.73\ m^2$	59.0±14.9	73.1±20.8	0.022
Corrected calcium, mg/dL	10.2±0.5	11.5±1.0	<0.001
Serum phosphate, mg/dL	3.2±0.5	2.7±0.5	0.001
ALP, U/L	222 (180-264)	273 (201-372)	0.102
BAP, μg/L	13.4 (10.2-20.2)	23.7 (18.3-34.5)	0.002
TRACP5b, mU/dL	347 (235-547)	663 (426-1067)	0.006
wPTH, pg/mL	46.3 (33.0-63.6)	140.5 (76.9-191.3)	<0.001
25OHD, ng/mL	18.0 (13.5-26.0)	10.9 (9.3-11.8)	0.001
$1,25(OH)_2D$, pg/mL	73.0 (52-113)	85.0 (66.0-131)	0.125
Uca/cr	0.15±0.07	0.26±0.11	0.001
%TRP, %	84.1±4.0	81.6±9.1	0.278
TBS	1.193±0.07	1.208±0.07	0.517
LS-BMD, g/cm^2	0.714±0.12	0.725±0.12	0.782
LS-BMD, T-score	-2.89±1.14	-2.71±1.17	0.617
FN-BMD, g/cm^2	0.520±0.07	0.517±0.08	0.912
FN-BMD, T-score	-2.50±0.63	-2.54±0.72	0.862
TH-BMD, g/cm^2	0.626±0.11	0.640±0.12	0.699

TH-BMD, T-score	-2.22±0.88	-2.09±0.99	0.696
Vertebral fracture, yes/no	2/17	1/18	1.000
Prior use of bisphosphonates, yes/no	10/9	11/8	1.000
Other indications for surgery			
Corrected calcium, yes/no	3/16	14/5	0.001
Renal involvement, yes/no	12/7	14/5	0.728
Nephrolithiasis, yes/no	1/18	13/6	0.001
eGFR <60 mL/min, yes/no	11/8	5/14	0.099
Age 50 years, yes/no	0/19	2/17	0.487

Values are expressed as number or %, mean ± SD, or median (interquartile range).

Abbreviations: Dmb, denosumab; PTX, parathyroidectomy; BMI, body mass index; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; BAP, bone alkaline phosphatase; TRACP-5b, tartrate-resistant acid phosphatase-5b; wPTH, whole parathyroid hormone; 25OHD, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; Uca/cr, urinary calcium creatinine ratio; %TRP, percentage of tubular reabsorption of phosphate; TBS, trabecular bone score; LS-BMD, lumbar spine bone mineral density; TH-BMD, total hip bone mineral density; FN-BMD, femoral neck bone mineral density

Table 2. Time course of changes in biochemistry data at baseline and at 12 months in both groups.

Biochemistry data		baseline	12 month
Corrected calcium, mg/dL	Dmb	10.2±0.5	10.3±0.4
	PTX	11.5±1.0$^{\#}$	9.4±0.6*
wPTH, pg/mL	Dmb	46.3 (33.0-63.6)	59.4 (47.6-88.6)*
	PTX	140.5 (76.9-191.3)$^{\#}$	33.0 (26.9-53.8)*
ALP, U/L	Dmb	222 (180-264)	154 (132-210)*
	PTX	273 (201-372)	163 (131-219)*
Serum phosphate, mg/dL	Dmb	3.2±0.5	3.0±0.6*
	PTX	2.7±0.5	3.3±0.6*
eGFR, mL/min/1.73 m^2	Dmb	59.0±14.9	59.3±16.8
	PTX	73.1±20.8$^{\#}$	64.6±13.6*

Values are expressed mean ± SD, or median (interquartile range).

*$p < 0.05$ for within group change between baseline and 12 months. $^{\#}p < 0.05$ for the baseline difference between the groups.

Abbreviations: Dmb, denosumab; PTX, parathyroidectomy; wPTH, whole parathyroid hormone; ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate

Table 3. Correlations between the percent changes in DXA parameters after 12 months and baseline bone turnover markers

Bone turnover marker		%LS-BMD		%TH-BMD		%FN-BMD		%TBS	
		ρ	p	ρ	p	ρ	p	ρ	p
ALP, U/L	Dmb	0.118	0.632	0.597	0.007	0.486	0.170	-0.267	0.270
	PTX	0.339	0.156	0.422	0.033	0.422	0.081	0.256	0.290
BAP, μg/L	Dmb	0.239	0.325	0.698	0.001	0.263	0.270	-0.356	0.135
	PTX	0.416	0.086	0.439	0.072	0.319	0.213	0.141	0.576
TRACP-5b, mU/dL	Dmb	0.358	0.133	0.705	0.001	0.154	0.340	-0.323	0.178
	PTX	0.618	0.006	0.770	0.001	0.520	0.033	0.158	0.532

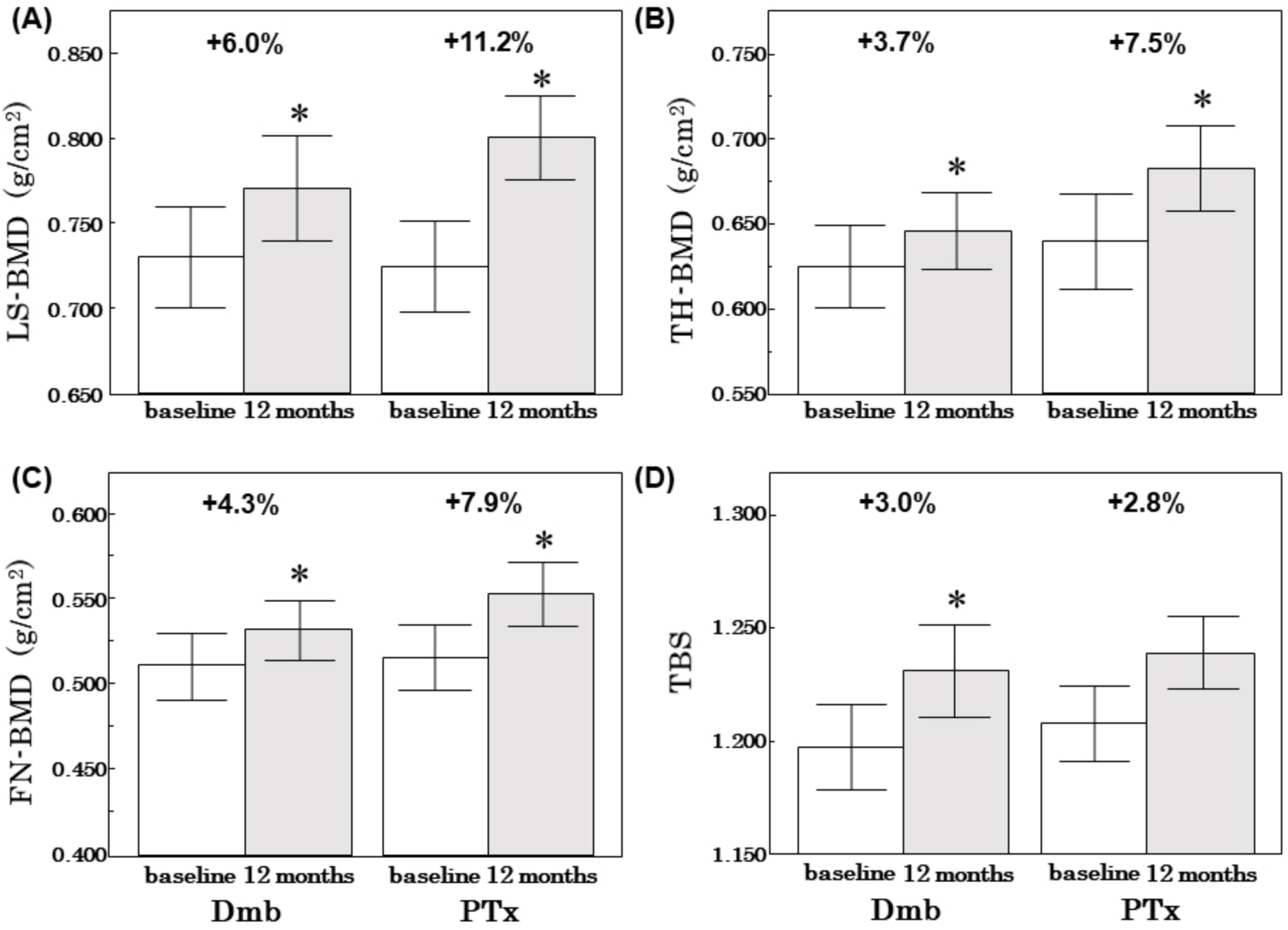
ρ Spearman's correlation coefficient.

Abbreviations: ALP, alkaline phosphatase; BAP, bone alkaline phosphatase; TRACP-5b, tartrate-resistant acid phosphatase-5b; Dmb, denosumab; PTX, Parathyroidectomy; LS-BMD, lumbar spine bone mineral density; TH-BMD, total hip bone mineral density; FN-BMD, femoral neck bone mineral density; TBS, trabecular bone score

Figure legends

Figure 1. LS-BMD (A), TH-BMD (B), FN-BMD (C), and TBS (D) at baseline and after 12 months in PHPT patients who received Dmb as compared to those who underwent PTX.

Values are presented as the mean ± SE. *p <0.05 for within group change between baseline and 12 months.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+6.0%
+11.2%
0.850
0.800
0.750
0.700
0.650
LS-BMD (g/cm²)
*
*
baseline 12 months
baseline 12 months
(B)
+3.7%
+7.5%
0.750
0.700
0.650
0.600
0.550
TH-BMD (g/cm²)
*
*
baseline 12 months
baseline 12 months
(C)
+4.3%
+7.9%
0.600
0.550
0.500
0.450
0.400
FN-BMD (g/cm²)
*
*
baseline 12 months
baseline 12 months
Dmb
PTx
(D)
+3.0%
+2.8%
1.300
1.250
1.200
1.150
TBS
*
baseline 12 months
baseline 12 months
Dmb
PTx

Fig. 1

References

1. Bilezikian, J.P., Bandeira, L., Khan, A., Cusano, N.E.: Hyperparathyroidism. Lancet **391**(10116), 168-178 (2018).
2. Bilezikian, J.P., Brandi, M.L., Eastell, R., Silverberg, S.J., Udelsman, R., Marcocci, C., Potts, J.T., Jr.: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab **99**(10), 3561-3569 (2014).
3. Wu, B., Haigh, P.I., Hwang, R., Ituarte, P.H., Liu, I.L., Hahn, T.J., Yeh, M.W.: Underutilization of parathyroidectomy in elderly patients with primary hyperparathyroidism. J Clin Endocrinol Metab **95**(9), 4324-4330 (2010).
4. Silva, B.C., Leslie, W.D., Resch, H., Lamy, O., Lesnyak, O., Binkley, N., McCloskey, E.V., Kanis, J.A., Bilezikian, J.P.: Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res **29**(3), 518-530 (2014).
5. Hans, D., Goertzen, A.L., Krieg, M.A., Leslie, W.D.: Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res **26**(11), 2762-2769 (2011).
6. Eller-Vainicher, C., Filopanti, M., Palmieri, S., Ulivieri, F.M., Morelli, V., Zhukouskaya, V.V., Cairoli, E., Pino, R., Naccarato, A., Verga, U., Scillitani, A., Beck-Peccoz, P., Chiodini, I.: Bone quality, as measured by trabecular bone score, in patients with primary hyperparathyroidism. Eur J Endocrinol **169**(2), 155-162 (2013).
7. Romagnoli, E., Cipriani, C., Nofroni, I., Castro, C., Angelozzi, M., Scarpiello, A., Pepe, J., Diacinti, D., Piemonte, S., Carnevale, V., Minisola, S.: "Trabecular Bone Score" (TBS): an indirect measure of bone micro-architecture in postmenopausal patients with primary hyperparathyroidism. Bone **53**(1), 154-159 (2013).
8. Marcocci, C., Bollerslev, J., Khan, A.A., Shoback, D.M.: Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. J Clin Endocrinol Metab **99**(10), 3607-3618 (2014).
9. Perazella, M.A., Markowitz, G.S.: Bisphosphonate nephrotoxicity. Kidney Int **74**(11), 1385-1393 (2008).
10. Yeh, M.W., Zhou, H., Adams, A.L., Ituarte, P.H., Li, N., Liu, I.A., Haigh, P.I.: The Relationship of Parathyroidectomy and Bisphosphonates With Fracture Risk in Primary Hyperparathyroidism: An Observational Study. Ann Intern Med (2016).
11. Jamal, S.A., Ljunggren, O., Stehman-Breen, C., Cummings, S.R., McClung, M.R., Goemaere, S., Ebeling, P.R., Franek, E., Yang, Y.C., Egbuna, O.I., Boonen, S., Miller, P.D.: Effects of denosumab on fracture and bone mineral density by level of kidney function. J

Bone Miner Res **26**(8), 1829-1835 (2011).

12. Eller-Vainicher, C., Palmieri, S., Cairoli, E., Goggi, G., Scillitani, A., Arosio, M., Falchetti, A., Chiodini, I.: Protective Effect of Denosumab on Bone in Older Women with Primary Hyperparathyroidism. J Am Geriatr Soc **66**(3), 518-524 (2018).
13. McClung, M.R., Lippuner, K., Brandi, M.L., Zanchetta, J.R., Bone, H.G., Chapurlat, R., Hans, D., Wang, A., Zapalowski, C., Libanati, C.: Effect of denosumab on trabecular bone score in postmenopausal women with osteoporosis. Osteoporos Int **28**(10), 2967-2973 (2017).
14. Koumakis, E., Souberbielle, J.C., Sarfati, E., Meunier, M., Maury, E., Gallimard, E., Borderie, D., Kahan, A., Cormier, C.: Bone mineral density evolution after successful parathyroidectomy in patients with normocalcemic primary hyperparathyroidism. J Clin Endocrinol Metab **98**(8), 3213-3220 (2013).
15. Genant, H.K., Jergas, M., Palermo, L., Nevitt, M., Valentin, R.S., Black, D., Cummings, S.R.: Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis The Study of Osteoporotic Fractures Research Group. J Bone Miner Res **11**(7), 984-996 (1996).
16. Imai, E., Horio, M., Nitta, K., Yamagata, K., Iseki, K., Tsukamoto, Y., Ito, S., Makino, H., Hishida, A., Matsuo, S.: Modification of the Modification of Diet in Renal Disease (MDRD) Study equation for Japan. Am J Kidney Dis **50**(6), 927-937 (2007).
17. Miyaoka, D., Imanishi, Y., Ohara, M., Hayashi, N., Nagata, Y., Yamada, S., Mori, K., Emoto, M., Inaba, M.: Impaired residual renal function predicts denosumab-induced serum calcium decrement as well as increment of bone mineral density in non-severe renal insufficiency. Osteoporos Int **30**(1), 241-249 (2019).
18. Castellano, E., Attanasio, R., Boriano, A., Borretta, G.: Clinical Presentation of Primary Hyperparathyroidism in Older Adults. J Endocr Soc **3**(12), 2305-2312 (2019).
19. Gianotti, L., Tassone, F., Cesario, F., Pia, A., Razzore, P., Magro, G., Piovesan, A., Borretta, G.: A slight decrease in renal function further impairs bone mineral density in primary hyperparathyroidism. J Clin Endocrinol Metab **91**(8), 3011-3016 (2006).
20. Makras, P., Polyzos, S.A., Papatheodorou, A., Kokkoris, P., Chatzifotiadis, D., Anastasilakis, A.D.: Parathyroid hormone changes following denosumab treatment in postmenopausal osteoporosis. Clin Endocrinol (Oxf) **79**(4), 499-503 (2013).
21. Hendrickson, C.D., Castro Pereira, D.J., Comi, R.J.: Renal impairment as a surgical indication in primary hyperparathyroidism: do the data support this recommendation? J Clin Endocrinol Metab **99**(8), 2646-2650 (2014).
22. Egan, R.J., Dewi, F., Arkell, R., Ansell, J., Zouwail, S., Scott-Coombes, D., Stechman, M.: Does elective parathyroidectomy for primary hyperparathyroidism affect renal function?

A prospective cohort study. Int J Surg **27**, 138-141 (2016).

23. Tassone, F., Guarnieri, A., Castellano, E., Baffoni, C., Attanasio, R., Borretta, G.: Parathyroidectomy Halts the Deterioration of Renal Function in Primary Hyperparathyroidism. J Clin Endocrinol Metab **100**(8), 3069-3073 (2015).
24. Garcia-Martin, F., Guadalix, S., Garcia-Boyano, F., Melon Pena, N., Martinez Pueyo, J.I., Callejas Martinez, R., Praga Terente, M.: Does renal function improve after parathyroidectomy in primary hyperparathyroidism? Nefrologia **39**(2), 160-167 (2019).
25. Block, G.A., Bone, H.G., Fang, L., Lee, E., Padhi, D.: A single-dose study of denosumab in patients with various degrees of renal impairment. J Bone Miner Res **27**(7), 1471-1479 (2012).
26. Miyaoka, D., Inaba, M., Imanishi, Y., Hayashi, N., Ohara, M., Nagata, Y., Kurajoh, M., Yamada, S., Mori, K., Emoto, M.: Denosumab Improves Glomerular Filtration Rate in Osteoporotic Patients With Normal Kidney Function by Lowering Serum Phosphorus. J Bone Miner Res **34**(11), 2028-2035 (2019).
27. Di Gregorio, S., Del Rio, L., Rodriguez-Tolra, J., Bonel, E., Garcia, M., Winzenrieth, R.: Comparison between different bone treatments on areal bone mineral density (aBMD) and bone microarchitectural texture as assessed by the trabecular bone score (TBS). Bone **75**, 138-143 (2015).
28. Miyaoka, D., Imanishi, Y., Ohara, M., Hayashi, N., Nagata, Y., Yamada, S., Mori, K., Emoto, M., Inaba, M.: Effects of Teriparatide and Sequential Minodronate on Lumbar Spine Bone Mineral Density and Microarchitecture in Osteoporosis. Calcif Tissue Int **101**(4), 396-403 (2017).
29. Ominsky, M.S., Libanati, C., Niu, Q.T., Boyce, R.W., Kostenuik, P.J., Wagman, R.B., Baron, R., Dempster, D.W.: Sustained Modeling-Based Bone Formation During Adulthood in Cynomolgus Monkeys May Contribute to Continuous BMD Gains With Denosumab. J Bone Miner Res **30**(7), 1280-1289 (2015).
30. Cipriani, C., Abraham, A., Silva, B.C., Cusano, N.E., Rubin, M.R., McMahon, D.J., Zhang, C., Hans, D., Silverberg, S.J., Bilezikian, J.P.: Skeletal changes after restoration of the euparathyroid state in patients with hypoparathyroidism and primary hyperparathyroidism. Endocrine **55**(2), 591-598 (2017).
31. Tay, Y.D., Cusano, N.E., Rubin, M.R., Williams, J., Omeragic, B., Bilezikian, J.P.: Trabecular Bone Score in Obese and Nonobese Subjects With Primary Hyperparathyroidism Before and After Parathyroidectomy. J Clin Endocrinol Metab **103**(4), 1512-1521 (2018).
32. Miguel, G.A., Carranza, F.H., Rodriguez, J.C.R., Ramos, M.A., Pablos, D.L., Herrero, E.F., Diaz-Guerra, G.M.: Trabecular Bone Score, Bone Mineral Density and Bone Markers in

Patients with Primary Hyperparathyroidism 2 Years After Parathyroidectomy. Horm Metab Res **51**(3), 186-190 (2019).

33. Nakchbandi, I.A., Lang, R., Kinder, B., Insogna, K.L.: The role of the receptor activator of nuclear factor-kappaB ligand/osteoprotegerin cytokine system in primary hyperparathyroidism. J Clin Endocrinol Metab **93**(3), 967-973 (2008).
34. Austin, M., Yang, Y.C., Vittinghoff, E., Adami, S., Boonen, S., Bauer, D.C., Bianchi, G., Bolognese, M.A., Christiansen, C., Eastell, R., Grauer, A., Hawkins, F., Kendler, D.L., Oliveri, B., McClung, M.R., Reid, I.R., Siris, E.S., Zanchetta, J., Zerbini, C.A., Libanati, C., Cummings, S.R., Trial, F.: Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. J Bone Miner Res **27**(3), 687-693 (2012).
35. Alonso, S., Ferrero, E., Donat, M., Martinez, G., Vargas, C., Hidalgo, M., Moreno, E.: The usefulness of high pre-operative levels of serum type I collagen bone markers for the prediction of changes in bone mineral density after parathyroidectomy. J Endocrinol Invest **35**(7), 640-644 (2012).