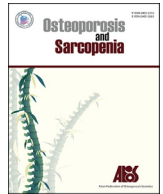




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Original article

## Utility of radius bone densitometry for the treatment of osteoporosis with once-weekly teriparatide therapy

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### ABSTRACT

**Objectives:** As clinics that treat patients with osteoporosis do not usually have central dual-energy X-ray absorptiometry (DXA), bone density is often measured with radial DXA. However, no long-term evidence exists for radius bone density outcomes following treatment with once-weekly teriparatide in actual medical treatment.

**Methods:** We evaluated changes in bone density at 6-, 12-, and 18-month intervals using radial DXA in patients treated with once-weekly teriparatide for more than 6 months.

**Results:** A significant increase in bone mineral density (BMD) was observed at the 1/3 and 1/10 radius sites 12 months after the initiation of once-weekly teriparatide. We also observed that the rate of change in BMD was greater at the distal 1/10 radius than at the 1/3 radius.

**Conclusions:** Considering these points, the effect of once-weekly teriparatide therapy can be observed at the radius. In clinics that do not have central DXA, but instead have radial DXA, these findings can help to evaluate the effect of once-weekly teriparatide treatment on osteoporosis.

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## 1. Introduction

Dual-energy X-ray Absorptiometry (DXA) is a type of bone densitometry that allows for differentiation between bone and soft tissue. It uses 2 X-ray beams of different energy levels. Accordingly, bone mass per unit area and bone mineral density (BMD) can be calculated by measuring the X-ray attenuation rate for each beam. BMD measurement using DXA is the gold standard for diagnosing osteoporosis and assessing treatment efficacy as it is very precise with minimal exposure to radiation [1]. Currently, the lumbar spine, femur, and radius are commonly used as measurement sites at the clinic. Japanese guidelines [1] recommend the use of the lumbar spine and the proximal femur for the assessment of bone density. Meanwhile, the radius is used for measurement only if the lumbar spine and proximal femur cannot be used. However, several medical centers do not have central DXA and instead measure bone density using radial DXA. This is because central DXA, which allows

for the measurement of the lumbar spine and proximal femur, is expensive and burdensome. Therefore, it is important to assess the change in bone density at the radial distal 1/10 site (abundant spongy bone) and 1/3 site (abundant cortical bone) and to confirm the utility of radial DXA in patients being treated for osteoporosis.

In this study, once-weekly teriparatide was used to assess radial BMD. Teriparatide increases bone density by inducing osteoblast proliferation and promoting bone formation. Although only daily self-injection formats are used abroad, once-weekly teriparatide is additionally marketed in Japan. Daily teriparatide has been reported to increase the bone density in the lumbar spine by 10% after 12 months of use in a phase III clinical trial in Japan, which is more effective than bisphosphonate treatment [2]. In this phase III clinical trial in Japan (Teriparatide Once Weekly Efficacy Research: TOWER Study) [3], once-weekly teriparatide increased bone density at the total proximal femur by 3.1% within 72 weeks of treatment, which resulted in a reduction in the incidence of vertebral fracture by 80%. Since the incidence of vertebral fracture was reduced by 65% after daily teriparatide use [4], once-weekly teriparatide is believed to more effectively reduce the relative risk of osteoporotic damage in comparison to other osteoporosis medications. Once-weekly teriparatide is only used in Japan and its

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time-course effect on radial bone density has only been measured up to 6 months after therapy initiation, as reported by Urushibara et al. [5]. These researchers documented a significant increase in BMD at the 1/10 radius site, but did not examine long-term efficacy and safety. Therefore, we performed this study to determine efficacy and safety of once-weekly teriparatide therapy over an 18-month period.

## 2. Methods

### 2.1. Study design

Retrospective study at a clinic in Japan. Subjects received a once-weekly subcutaneous injection of 56.5- $\mu$ g teriparatide for 18 months. The primary doctor measured BMD at all 3-time points by using radial DXA. Moreover, Institutional Review Board (IRB) approval of the protocol was in place prior to the study.

### 2.2. Study subjects

Patients that met the following requirements were included in the safety evaluation:

- (1) Patients with osteoporosis
- (2) Patients that initiated once-weekly teriparatide (56.5  $\mu$ g/dose) therapy after 2011.

Among those that satisfied the aforementioned criteria, we included those that met the following conditions in the efficacy evaluation:

- (1) Measurement using radial DXA was available at the time of dosing.
- (2) Once-weekly teriparatide was administered for more than 6 months.
- (3) BMD at the radial distal 1/3 site was 70% or more below the young adult mean value at its baseline.
- (4) Radial DXA images were taken at 6, 12, or 18 months.
- (5) The same part was measured in the study, such as the primary doctor was able to judge that the length of the forearm was measured equally and rotation of the arm was not detected.

### 2.3. Treatments

We evaluated the change in bone density at the radial distal 1/10 site (abundant spongy bone) and at the radial distal 1/3 site (abundant cortical bone) over time at the baseline and at 6, 12, and 18 months in patients treated with once-weekly teriparatide.

### 2.4. Evaluation

Safety endpoint: Adverse events that occurred during the study period were evaluated.

Efficacy endpoint: The primary endpoint was change in bone density (distal 1/3 site) after 18 months measured using radial DXA (Dichroma Scan DCS-600EXV, Hitachi Ltd., Tokyo, Japan) for all data. Secondary endpoints were change/rate of change (distal 1/3 site and 1/10 site) of bone density at 6, 12, and 18 months (excluding primary endpoint).

### 2.5. Statistical analysis

Change in BMD from the baseline was evaluated using a paired

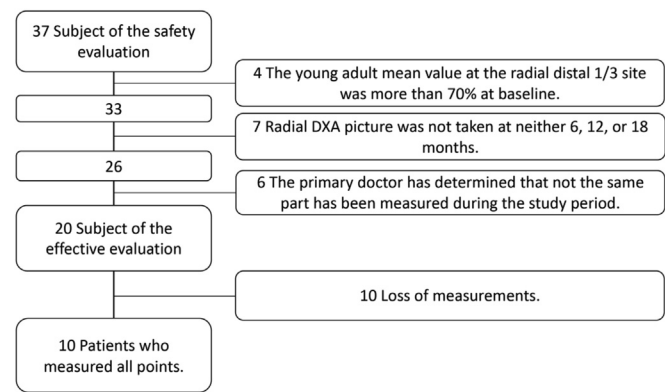


Fig. 1. Participant flow. DXA, Dual-energy X-ray absorptiometry.

*t*-test without considering multiplicity. The rate of change in BMD from the baseline was analyzed using data for which all measurements, from the baseline to 18 months, were available. The correlation between BMD at the 1/10 and 1/3 radius sites was evaluated using Pearson test. Results of the analysis in the full text are expressed as the mean  $\pm$  standard deviation for continuous variables and number of cases (%) on a nominal scale. A 2-sided significance level of 5% was used. JMP ver. 13.1.0 (SAS Institute Inc., Cary, NC, USA), was used for statistical analysis.

### 2.6. Ethics statement

Although this was a retrospective observational study with anonymization in an unlinkable fashion, written informed consent was obtained from patients after our oral explanation.

This study was conducted with the approval of the ethics committee of the Adachi Kyosai Hospital (March 24th, 2016) (approval number: 2154). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## 3. Results

The participant inclusion flow chart is shown in Fig. 1. The baseline characteristics is shown in Table 1. Thirty-seven patients (all female) were evaluated for safety. The mean age of the patients was  $77.2 \pm 4.4$  years old. Of the 37 patients, 28 (75.7%) were undergoing concomitant vitamin D treatment. Change in BMD is

Table 1  
Baseline characteristics.

Characteristic	Subject of the safety evaluation (n = 37)	Patients who measured all points (n = 10)
Age, yr	77.2 $\pm$ 4.4	76.6 $\pm$ 3.4
Height, cm	147.4 $\pm$ 4.6	147.6 $\pm$ 4.0
Body weight, kg	47.2 $\pm$ 6.3	47.6 $\pm$ 2.2
Body mass index, kg/m <sup>2</sup>	21.7 $\pm$ 2.4	21.9 $\pm$ 1.2
Therapeutic agent before study (include overlap)		
Minodronic acid hydrate	13 (35.1)	4 (40.0)
Ibandronate sodium hydrate	3 (8.1)	0 (0)
Other bisphosphonate	8 (21.6)	4 (40.0)
SERM	8 (21.6)	2 (20.0)
Activated vitamin D	28 (75.7)	7 (70.0)
Calcitonin	21 (56.8)	3 (30.0)

Values are presented as mean  $\pm$  standard deviation or number (%). SERM, selective estrogen receptor modulators.

**Table 2**  
Values and changes of BMD at the distal radius in patients who measured all points (n = 10).

Duration, mo	1/3 radius BMD (g/cm <sup>2</sup> )		1/10 radius BMD (g/cm <sup>2</sup> )	
	Mean ± SD	P-value	Mean ± SD	P-value
0	0.357 ± 0.055	—	0.227 ± 0.046	—
6	0.360 ± 0.050	—	0.232 ± 0.044	—
12	0.361 ± 0.054	—	0.233 ± 0.044	—
18	0.362 ± 0.050	—	0.234 ± 0.043	—
Δ6	0.003 ± 0.012	0.429	0.005 ± 0.007	0.065
Δ12	0.004 ± 0.004	0.021*	0.005 ± 0.009	0.082
Δ18	0.005 ± 0.011	0.156	0.007 ± 0.009	0.046*

BMD, bone mineral density; SD, standard deviation.  
\*P < 0.05 vs. 0 month paired t-test.

shown in Table 2. While studying efficacy, we found that BMD at the 1/3 and 1/10 radius sites increased significantly after 12 months and 18 months, respectively. The rates of change in BMD at the 1/3 and 1/10 radius sites are shown in Fig. 2 for all cases that had data at 6, 12, and 18 months. It was observed that the rate of change in BMD was greater at the distal 1/10 radius than at the 1/3 radius.

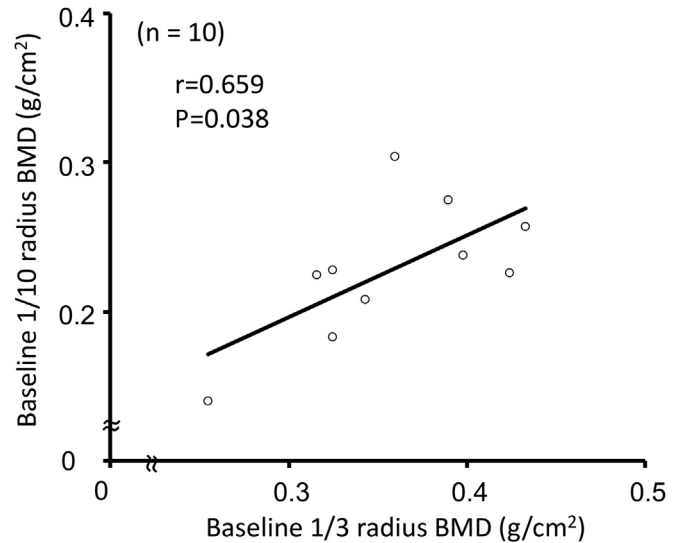
A significant, positive correlation was observed between the BMD at the 1/3 radius site and at the 1/10 radius site (Fig. 3).

In 5 of 37 cases, adverse events may have been causally related to teriparatide use (6 events, including 5 events of nausea and 1 event of pyrexia). Four of the 5 events of nausea were resolved following administration of an antiemetic agent, while the remaining event of nausea and 1 event of pyrexia resolved with rest. All of these events were not serious.

**4. Discussion**

In the patients who were measured at all follow-up points, there was a significant increase in BMD at the distal 1/3 radius at 12 months and at the distal 1/10 radius at 18 months. Although, there was an upward trend in BMD, there were no significant differences at some follow-up points.

Urushibara et al. [5] reported that no significant change in BMD at the 1/3 radius site was observed; while a significant increase in BMD at the 1/10 radius site was observed 6 months after initiation of once-weekly teriparatide. This suggests that the regimen increased the radius BMD regardless of timing. Recently, Sugimoto et al. [6] reported that a significant increase was observed in BMD at the 1/10 radius site at 24 and 104 weeks after initiation of once-weekly teriparatide. Sugimoto’s report was part of a clinical trial for an approval application, while our clinical trial was the result of actual medical treatment. The fact that a significant increase was observed in both types of clinical trials will support the use of once-

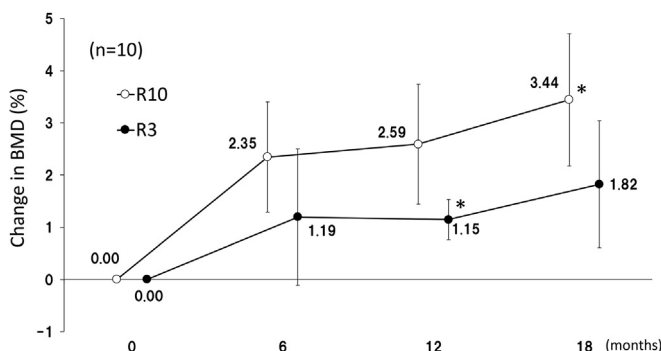


**Fig. 3.** Correlation of 1/3 radius bone mineral density (BMD) and 1/10 radius BMD at baseline.

weekly teriparatide.

The effect of daily teriparatide use on radial BMD has been reported previously. The consensus of these reports was that there has been a mild decrease in radial BMD following teriparatide use. Neer et al. [4] reported a 2% decrease in BMD in the shaft of the radius following administration of 40 µg of teriparatide during a 21-month observation period using DXA. Michalska et al. [7] reported that they evaluated the effect of daily teriparatide using DXA at the radial distal 1/3 site and observed a significant decrease in BMD by 2%–3% after 6 months. Macdonald et al. [8] reported that daily teriparatide decreased BMD at the radial distal site based on evaluation using high resolution peripheral quantitative computed tomography. The decreased BMD at this radial distal site following daily teriparatide use may be associated with increased porosity and thickness of cortical bone, the formation/addition of new bone matrix, thereby resulting in an apparent decrease in BMD. Zanchetta et al. [9] reported that compared with a placebo, patients treated with daily administration of teriparatide had significant increases in total bone mineral content and total bone area at the 15% distal radius site without significant increase in BMD. However, a significant increase in BMD was observed at both the 1/3 and 1/10 radius sites within 12 months after the initiation of once-weekly teriparatide. Urinary cross-linked N-telopeptides of type I collagen, an index of bone absorption, decreased by 5% following a once-weekly regimen, according to a report by Nakamura et al. [3], but increased by 50% following a daily regimen, according to a report by McClung et al. [10]. Therefore, Urushibara et al. [5] suggested that differences in the bone absorption property between daily regimen and once-weekly regimen could lead to differences in BMD. Since this study did not include a blood test, we are unable to comment on the bone absorption property; however, this is likely to influence the difference in BMD change.

Then, we compared the result of this study with the report by Urushibara et al. [5], which found that BMD at the 1/10 radius site increased significantly at 6 months. In this analysis, no significant change was observed after 6 months, while a significant increase in BMD was observed at the 1/3 and 1/10 radius sites after 12 months. Although there was a delay before this significant difference could be detected, an improvement in radial BMD was similarly observed, thereby supporting the use of once-weekly teriparatide. Compared with the study reported by Urushibara et al. [5]. The fact that the



**Fig. 2.** Percent changes in bone mineral density (BMD) at the distal radius. Data are mean ± standard error. \*P < 0.05 vs. 0 month paired t-test.

number of patients is larger in this study seems to be the reason for the difference in the period during which significant difference was observed (in this study, 10 subjects; Urushibara's study, 5 subjects).

A review of the rate of change in BMD at the distal 1/3 radius and 1/10 radius revealed that the rate of change in BMD increased more at the distal 1/10 radius than at the distal 1/3 radius. Urushibara et al. [5] reported a significant 1.98% increase in BMD at the 1/10 radius site and an upward trend of 0.98% in BMD at the 1/3 radius site within 6 months after the initiation of once-weekly teriparatide. Conventionally, BMD at the distal 1/10 radius was considered to have poor measurement reproducibility compared to the distal 1/3 radius. However, along with the evolution of measurement technology, recently reproducibility has improved even at the distal 1/10 radius. If similar measurement reproducibility can be expected, we will be able to detect the change of BMD at the distal 1/10 radius sooner. The radial distal 1/10 site has abundant spongy bone and teriparatide is known to increase the bone mass of spongy bone instead of cortical bone [11]. In this way, the effect of once-weekly teriparatide is considered to be greater at the 1/10 radius site. In this study, we observed a correlation between BMD at the 1/3 radius site and 1/10 radius site. Although guidelines do not recognize BMD at the 1/10 radius site as a standard method for diagnosing and assessing the effect of treatment for osteoporosis, our study results suggest that BMD at the 1/10 radius site can be an optional index, particularly in investigating the effect on spongy bone.

Our results revealed an increase in radial bone density 12 months after initiation of once-weekly teriparatide. This finding will be helpful in evaluating the efficacy of once-weekly teriparatide treatment to treat osteoporosis, as indicated by radial DXA.

Since this was a retrospective observational study that only contained data from patients that were able to continue treatment, it is possible that we introduced bias during patient selection. This study was also limited by our inability to compare the results of teriparatide treatment with other pharmaceutical drugs as this was a single-arm study. Nevertheless, we assessed safety in all patients without bias during the study period.

## 5. Conclusion

A significant increase in BMD was observed at both the 1/3 and 1/10 radius sites at 12 months after the initiation of once-weekly teriparatide treatment in patients with osteoporosis. Therefore, once-weekly teriparatide could be effective in treating osteoporosis, as indicated by its effect on the radius. Significant positive correlation was observed between BMD at the 1/3 radius site and BMD at the 1/10 radius site. Furthermore, the rate of change in BMD at the 1/10 radius site could be an early indicator of improvement. In clinics that do not have central DXA, but instead have radial DXA, it may be helpful to evaluate the treatment effect of once-weekly teriparatide on osteoporosis.

## Conflicts of interest

Harumi Nakayama has received a research grant from Asahi

Kasei Pharma Corporation. Teruki Sone has received research grants from Asahi Kasei Pharma, Astellas Pharma, Daiichi-Sankyo, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Pfizer and Teijin Pharma, and consulting fees from Daiichi-Sankyo and Takeda Pharmaceutical. Except for that, no potential conflict of interest relevant to this article was reported.

## Acknowledgments

This study was conducted with financial support from the Asahi Kasei Pharma Corporation. However, the Asahi Kasei Pharma Corporation only provided funding and academic advice, and it was not involved in the management or analysis of our data.

We would like to express our sincere gratitude to Mr. Hiroaki Suzuki (Asahi Kasei Pharma Corporation) for scientific advice, including references for revising the manuscript. We also would like to thank Nouvelle Place Inc. for conducting the data analyses.

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