Case Report

Bone microstructure changes due to once-/twice-weekly teriparatide administration: A report of five cases using high-resolution peripheral quantitative computed tomography

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Abstract

This study was conducted with the aim of presenting cases in which high-resolution peripheral quantitative computed tomography (HR-pQCT) was used to investigate changes in bone microstructure due to once-weekly/twice-weekly administration of teriparatide (TPTD). Of osteoporosis patients who participated in a non-inferiority trial (TWICE study: once-weekly vs twice-weekly TPTD) with lumbar bone mineral density (BMD) as the primary endpoint, five cases scanned by HR-pQCT before TPTD administration were analyzed. Two cases were given once-weekly TPTD, three were given twice-weekly TPD, and HR-pQCT was repeated after 48 weeks. A sufficient anabolic effect of once-weekly/twice-weekly TPTD on the trabecular and cortical bone at the tibia was obtained. In addition, the average change in cortical porosity (Ct.Po) was only 0.3% in the tibia and
0.2% in the radius. These findings indicate that once-weekly and twice-weekly TPTD can be expected to improve bone microstructure, and the increase in Ct.Po may be suppressed.

Keywords: Teriparatide, Osteoporosis, Cortical porosity, High-resolution peripheral quantitative computed tomography, Bone

Introduction

High-resolution peripheral quantitative computed tomography (HR-pQCT) can be used to analyze the detailed bone microstructure of trabecular bone and cortical bone over time. Some HR-pQCT studies have already demonstrated the changes in bone microstructure after daily teriparatide (TPTD) [1-3], but there have been no reports of the use of HR-pQCT to examine the effect of once-weekly/twice-weekly administration of TPTD, which was developed in Japan, on bone microstructure. Using HR-pQCT, the aim was to evaluate the effects of once-weekly/twice-weekly TPTD administration on the bone microstructure of five osteoporosis patients who participated in a non-inferiority trial (TWICE study: once-weekly vs twice-weekly TPTD), with lumbar bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) as the primary endpoint.

Case presentations

This study was approved by the Ethics Review Committee for Clinical Research of Nihonbashi Sakura Clinic. HR-pQCT was performed at our institution before the 48-week, multicentre, randomized, double-blind, double-dummy, active-controlled, non-inferiority trial conducted in Japan (TWICE study) (JapicCTI-163477) [4,5], and then changes in bone microstructure due to TPTD were examined by HR-pQCT in 5 subjects who participated in the TWICE study and consented to participate in the present study. The subjects were randomly allocated to either TPTD 28.2 μg twice weekly and placebo once weekly (28.2-μg twice-weekly group) or TPTD 56.5 μg once weekly and placebo twice weekly (56.5-μg once-weekly group).

The primary endpoint was the changes in bone microstructure parameters at the radius and tibia on HR-pQCT. HR-pQCT was performed before the start (week 0) and after the end of the TWICE study (week 48). Each subject’s nondominant distal radius and tibia were scanned by second-generation HR-pQCT (Xtreme CT II, Scanco Medical AG, Brütisellen, Switzerland) to assess bone microstructure. The HR-pQCT imaging protocol and settings were as reported by Chiba et al [6]. The measured parameters were: total BMD (Tt.BMD;
mgHA/cm³), trabecular BMD (Tb.BMD; mgHA/cm³), cortical BMD (Ct.BMD; mgHA/cm³), trabecular area (Tb.Ar; mm²), trabecular bone volume fraction (Tb.BV/TV; %), trabecular number (Tb.N; 1/mm), trabecular thickness (Tb.Th; mm), trabecular separation (Tb.Sp; mm), inhomogeneity of the trabecular network (Tb.1/N.SD; mm), cortical area (Ct.Ar; mm²), cortical thickness (Ct.Th; mm), cortical perimeter (Ct.Pm; mm), cortical porosity (Ct.Po; %), and cortical pore diameter (Ct.Po.Dm; mm) [7]. The secondary endpoints were the percentage changes from baseline in BMDs at the lumbar spine (L2-4), total hip, and femoral neck, and bone turnover markers. Study procedures for DXA and blood tests were conducted as described earlier [4].

Two cases were assigned to the once-weekly group (A, B), and three were assigned to the twice-weekly group (C, D, E). Their ages ranged from 67 to 84 years, with case A being the oldest and case B being the youngest. Case C had the lowest body mass index and the lowest BMDs. Case D was the only male. In case E, the BMDs were the highest, whereas the serum 25-hydroxyvitamin D3 level was 21.7 ng/ml, which was the only one less than 30 ng/ml (Table 1).

The changes in HR-pQCT parameters in the tibia, which is a loaded bone, are summarized in Supplementary Table 1. There were no significant changes in Tt.BMD, Tb.BMD, and Ct.BMD after TPTD administration, but the change rate of Ct.BMD tended to decrease with once-weekly TPTD administration (bold in Supplementary Table 1). Regarding the indices of trabecular bone microstructure, BV/TV increased in 4 cases, Tb.N increased in all cases, Tb.Sp decreased in all cases, and Tb.1/N.SD decreased in 4 cases (Figure 1A); the absolute value of the change rate tended to be larger with twice-weekly TPTD administration (bold in Supplementary Table 1). Ct.Th was increased in 4 cases, although there was little change of cortical bone microstructure parameters. The average absolute change in Ct.Po in the tibia was 0.26% (range, -0.3% to 1.6%) (Figure 1A, bold in Supplementary Table 1).

Changes in HR-pQCT parameters in the radius, which is an unloaded bone, are summarized in Supplementary Table 2. The mean values of Tt.BMD and Tb.BMD remained unchanged after TPTD administration, but Ct.BMD decreased in all cases (bold in Supplementary Table 2). The mean values of BV/TV, Tb.Ar, and Tb.Th did not change after TPTD administration, whereas the change rate of Tb.N tended to decrease, and the change rates of Tb.Sp and Tb.1/N.SD tended to increase only with once-weekly TPTD administration (Figure 1B, bold in Supplementary Table 2). The average absolute change of Ct.Po in the radius was 0.16% (range, 0% to 0.3%) (Figure 1B, bold in Supplementary Table 2).

The average lumbar BMD change at 24 and 48 weeks after TPTD administration was 4.6% (range, -0.2% to 8.7%) and 7.6% (range, -0.8% to 11.2%), respectively, whereas the average total hip BMD change was
1.4% (range, -3.5% to 8.1%) and -0.1% (range, -5.7% to 4.3%), respectively, and the average femoral neck BMD change was 0.1% (range, -3.4% to 3.8%) and -0.3% (range, -6.8% to 3.3%), respectively.

Serum levels of osteocalcin and type I procollagen-N-propeptide (P1NP), which are bone formation markers, increased at 4 or 12 weeks after TPTD administration in all cases, and they then tended to decrease gradually. Serum/urine type I collagen cross-linked N-telopeptide (NTX) and serum type I collagen cross-linked C-telopeptide (CTX), bone resorption markers, tended to decrease compared to baseline.

Discussion

The effects of once-weekly/twice-weekly TPTD on trabecular and cortical bone microstructure were investigated by HR-pQCT. There have been no reports evaluating changes in bone microstructure with once-weekly/twice-weekly TPTD. All five of the present cases participated in the TWICE study [4], and the changes in bone turnover markers and BMDs measured by DXA were mostly the same as those in the TWICE study [4]. Therefore, the results of the preliminary HR-pQCT analyses of 5 cases are presented as representative cases in which the effects of weekly TPTD and twice-weekly TPTD administration on trabecular and cortical bone microstructure were examined.

In general, it has been noted that TPTD administration increases Ct.Po, which likely reflects the increase in bone remodelling due to TPTD administration. The values of bone turnover markers, both bone formation and bone resorption markers, in patients treated with daily TPTD are elevated, indicating so-called high-turnover bone metabolism dynamics. The increase in Ct.Po after TPTD administration is considered to be due to the increase in the number of newly formed osteons, and it can be interpreted that new bones are being formed one after another. However, at the same time, there is concern that the mechanical strength of the long bone will decrease due to the increased Ct.Po [1]. The changes in bone turnover markers of once-weekly/twice-weekly TPTD verified by the TWICE study are characterized by increased bone formation markers, but decreased bone resorption markers, and it is presumed that the effect on bone resorption is small. The five cases investigated participated in the TWICE study, and the changes in bone turnover markers in the present study show the same tendency as in the TWICE study. In terms of bone microstructure parameters on HR-pQCT, compared to daily TPTD, once-weekly/twice-weekly TPTD tended to show a lesser increase in Ct.Po (the absolute change in the tibial Ct.Po in the present study was 0.26%, and the absolute change in radial Ct.Po was 0.16%; the absolute change in tibial Ct.Po from before to after daily TPTD administration was 0.33% [3], 0.49% [2], and 1.1% [1], respectively, and the absolute change in radial Ct.Po was 0.34% [3], 0.59% [2], and 0.7% [1], respectively.
respectively), and similar to the findings of bone turnover markers; it was thought that the effect on bone resorption was less than that of daily TPTD.

As mentioned above, bone turnover appeared lower with once-weekly/twice-weekly TPTD than with daily TPTD, but the anabolic effect of TPTD on trabecular and cortical bone at the tibia was sufficient (BV/TV increase, Tb.Sp, Tb.1/N.SD decrease, Ct.Th increase). Unfortunately, there were no findings suggestive of improvement in bone microstructure of the radius, but that is similar to the daily TPTD findings that the anabolic effect of TPTD on bone microstructure was more pronounced in the tibia, a loaded bone, and the once-weekly/twice-weekly TPTD is not altogether inferior to daily TPTD. In addition, the increase of hypocalcified bone due to the activation of remodelling might be the reason for the lack of increase in Tb.BMD and Tb.BV/TV, and this is a limitation of bone microstructure detection using HR-pQCT. In the tibia, the bone microstructure of trabecular and cortical bone is improved, and, as described above, the amount of increase in Ct.Po due to once-weekly/twice-weekly TPTD is small, so that a greater effect than that of daily TPTD can be expected. Since once-weekly/twice-weekly TPTD is administered less frequently than daily TPTD, it may be a more appropriate administration frequency considering the burden of injection for osteoporosis patients.

There were several limitations in this study. A specialist in HR-pQCT measurement provided guidance in the measurement of Tb.BMD and Tb.BV/TV to a certain standard. The measurement error at our institution was not evaluated in the present study, but there is no reason to believe that the error is not comparable to that of other researchers. Although this study included a small number of patients, the results suggest that the bone microstructure improvement effect of once-weekly/twice-weekly TPTD can be expected to be the same or greater than that of daily TPTD. Future investigations to determine the appropriate TPTD administration frequency (once-weekly, twice-weekly, daily) are needed.

**Conclusion**

There have been no previous reports of the use of HR-pQCT to evaluate the effects of once-weekly/twice-weekly TPTD on bone microstructure. In this study, bone microstructure was evaluated before and after TPTD administration in 5 osteoporosis patients who participated in the TWICE study. The effect of once-weekly/twice-weekly TPTD to improve bone microstructure can be expected to be the same as that of daily TPTD, and once-weekly/twice-weekly TPTD may suppress the increase in Ct.Po more than daily TPTD.
Funding
This research was supported by Asahi Kasei Pharma Corporation.

Conflicts of interest
Y. Ikejiri, M. Mori, T. Yoshioka, Kei Asano, M. Tsukamoto, Y. Yamanaka, and M. Kawasaki declare that they have no conflict of interest. N. Okimoto has received consulting fees from Asahi-Kasei Pharmaceutical Co., Ltd and Teijin Pharma Ltd. NO has received payments for lectures, including speakers’ bureau fees, from Asahi-Kasei Pharmaceutical Co., Ltd., Amgen Astellas BioPharma K.K., Astellas Pharma Inc., Chugai Pharmaceutical Co., Daiichi-Sankyo Co. Ltd., Eisai Co., Ltd., and Eli Lilly Japan. A. Sakai has received grants from Asahi-Kasei Pharmaceutical Co., Ltd. and Chugai Pharmaceutical Co., Ltd. during the conduct of the study, and personal lecture fees from Asahi-Kasei Pharmaceutical Co., Ltd. and Chugai Pharmaceutical Co., Ltd. HS, TY, and TU are employees of Asahi Kasei Pharma.

Consent to participate
All patients provided consent to participate in the present study.

Consent for publication
Study participants signed informed consent forms for publication.

References


Legends

Figure 1. Changes in representative bone microstructure parameters

(A) The top row shows the changes in bone microstructure parameters in the tibia, and (B) the bottom row shows the changes in bone microstructure parameters in the radius.

Table 1

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Group in the TWICE study</th>
<th>56.5-μg once-weekly TPTD</th>
<th>28.2-μg twice-weekly TPTD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Age, y</td>
<td>84</td>
<td>67</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Height, cm</td>
<td>150.6</td>
<td>148.3</td>
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<tr>
<td>Weight, kg</td>
<td>44.5</td>
<td>51</td>
</tr>
<tr>
<td>Body mass index, kg/m^2</td>
<td>19.6</td>
<td>23.2</td>
</tr>
<tr>
<td>Lumbar YAM, %</td>
<td>72.4</td>
<td>62.8</td>
</tr>
<tr>
<td>Femoral neck YAM, %</td>
<td>53.5</td>
<td>62.9</td>
</tr>
<tr>
<td></td>
<td>63.7</td>
<td>73.7</td>
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<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td>Total hip YAM, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-OH vitamin D₃, ng/mL</td>
<td>55.9</td>
<td>33.2</td>
</tr>
<tr>
<td>Serum osteocalcin, ng/mL</td>
<td>19.6</td>
<td>22.4</td>
</tr>
<tr>
<td>Serum P1NP, µg/L</td>
<td>41.2</td>
<td>33</td>
</tr>
<tr>
<td>Serum NTX, nmol BCE/L</td>
<td>14.9</td>
<td>16.7</td>
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<tr>
<td>Urinary NTX, nmol BCE/mmol Cr</td>
<td>35.1</td>
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</tr>
<tr>
<td>Serum CTX, ng/mL</td>
<td>0.33</td>
<td>0.24</td>
</tr>
</tbody>
</table>

**TPTD:** teriparatide, **YAM:** young adult mean, **P1NP:** type I procollagen-N-propeptide, **NTX:** type I collagen cross-linked N-telopeptide, **CTX:** type I collagen cross-linked C-telopeptide, **BCE:** bone collagen equivalents, **Cr:** creatinine.