



# The Effect of Teriparatide on the Hip: A Literature Review

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Teriparatide (TPTD) is a bone-forming agent used to treat postmenopausal osteoporosis. Since hip fractures are related to higher morbidity and mortality rates than other fractures, efficacious osteoporosis drugs for the hip are critical. We reviewed research articles reporting the efficacy of TPTD in terms of bone mineral density (BMD), fractures prevention, changes in the outer diameter, cortical thickness and porosity, post-operative periprosthetic BMD loss, and healing of typical and atypical fractures of the hip. Data meta-analyses indicated that TPTD not only increased the BMD of the proximal femur but also decreased the risk of hip fractures. Even though TPTD increases the cortical bone porosity of the proximal femur, the bone strength does not decrease as the majority of the porosity is located at the endocortex; further, it increases the outer diameter and thickens the cortical bone. TPTD stimulates bone remodeling and facilitates callus maturity and fracture healing. There have been many reports on improving the effect of TPTD on the healing of atypical fractures; therefore it is advisable to use TPTD considering the increase benefit compared to the risk.

**Key Words:** Parathyroid hormone, Teriparatide, Osteoporosis, Hip fractures, Hip

## INTRODUCTION

Teriparatide (TPTD) is a bone-forming agent used to treat postmenopausal osteoporosis. TPTD is recommended in the newly updated 2020 Endocrine Society guideline<sup>1)</sup> as first-line therapy in patients at very high risk of fractures, such

as those with severe osteoporosis (i.e., low T-score  $< -2.5$  and fractures) or multiple vertebral fractures. Considering the high morbidity and mortality rates linked to hip fractures, highly efficacious osteoporosis drugs are crucial<sup>2)</sup>. Many studies have focused on the use of TPTD for vertebral fractures; however, research or reviews focusing on their application for hip are rare<sup>3-5)</sup>. The reason for fewer studies is the relatively lower incidence of hip fracture, making it difficult to obtain statistical power for fracture prevention in a two-year prospective study, given the time for which TPTD is licensed to be used; additionally, there has been limited observation of the cortical bone that is a key structure for the strength of the hip<sup>6,7)</sup>. The importance of cortical bone and bone quality was recognized recently through the use of improved research methods. In this review, we describe the effect of TPTD on bone mineral density (BMD) and fracture prevention as well as on the expansion of outer diameter, thickness, and porosity of cortical bone, healing in typical and atypical fractures, and stability of the femoral stem.

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Synthetic parathyroid hormone (PTH) discussed in this article serves as the TPTD injected subcutaneously once a day.

## MECHANISMS OF ACTION

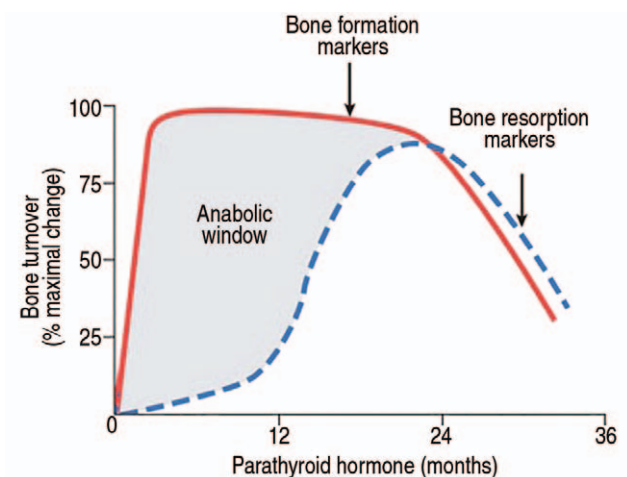
Although TPTD influences both bone formation and bone resorption, it activates osteoblasts more than osteoclasts. An interesting characteristic of TPTD is a temporal uncoupling between bone turnover markers. Initially, bone formation markers rise rapidly after therapy with TPTD has started. Several months thereafter, bone resorption markers increase. The time between the major gains in indices in bone formation and the subsequent increase in bone resorption markers can be described as the “anabolic window” (Fig. 1)<sup>8,9</sup>. There are three morphological characteristics of bone formation of TPTD: double labels overlying a scalloped cement line representing remodeling-based formation (RBF), those overlying a smooth cement line representing modeling-based formation (MBF), and formation over smooth cement lines adjacent to scalloped reversal lines representing an overflow MBF (oMBF) (Fig. 2)<sup>10,11</sup>.

## EFFECTS ON THE BMD OF THE HIP

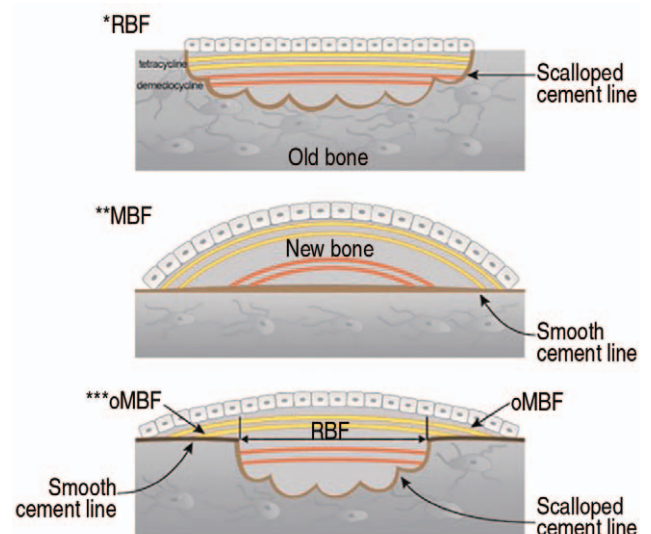
There have been many reports of improved hip BMD after using TPTD. In the Fracture Prevention Trial (FPT), the femoral neck BMD of the group that received 20  $\mu\text{g}$  of TPTD daily for 21 months increased by 3.5% ( $2.8 \pm 5.7\%$ ,

$P < 0.001$ ) compared with that of the placebo group ( $-0.7 \pm 5.4\%$ ); the total hip BMD increased by 3.6% ( $2.6 \pm 4.9\%$ ,  $P < 0.001$ ) compared with that of the placebo group ( $-1.0 \pm 4.3\%$ )<sup>9</sup>. In the Forteo Alendronate Comparator Trial (FACT) double-blind study, patients were divided into 2 groups; one received 20  $\mu\text{g}$  of TPTD and the other received 10 mg of alendronate daily for 18 months. BMD increased by 3.9% from the baseline value in patients who received TPTD, while BMD increased by 3.5% from the baseline value in those who received alendronate. There was no significant difference between the two groups ( $P > 0.05$ )<sup>12</sup>.

The FPT was brought to an early closure in 1998 because of osteosarcoma observed in a long-term carcinogenicity study in rats treated daily with TPTD. Notably, TPTD is licensed for use for 24 months. While TPTD reduced the risk of nonvertebral fragility fractures for up to 30 months after discontinuation of treatment, the total hip and femoral neck BMD decreased in TPTD-treated patients who received no follow-up treatment<sup>13</sup>. Sequential therapy, such as with bisphosphonate, is needed to preserve or increase BMD following treatment with TPTD in the lumbar spine, total hip, and femoral neck<sup>13</sup>. Sequential raloxifene prevented rapid bone loss at the lumbar spine and further increased BMD at the femoral neck, regardless of whether it was started immediately or after a one-year delay following TPTD treatment<sup>14</sup>. In studies where patients were treated with a bis-



**Fig. 1.** Changes in bone markers during the anabolic window. Bone formation markers increase more rapidly and earlier during the course of therapy than those reflecting bone resorption. Modified from the article of Pazianas [Trends Endocrinol Metab. 2015;26:111-3]<sup>8</sup> with original copyright holder's permission.



**Fig. 2.** Types of bone formation assessed with quadruple labeling. Shown are schematic illustrations of \*remodeling-based formation (RBF), \*\*modeling-based formation (MBF), and \*\*\*overflow modeling-based formation (oMBF). Modified from the article of Dempster et al. [J Bone Miner Res. 2018;33:298-306]<sup>10</sup> with original copyright holder's permission.

phosphonate (alendronate, risedronate) or denosumab, hip BMD decreased 6-12 months after switching to TPTD<sup>15-17</sup>.

### PREVENTIVE EFFECTS ON HIP FRACTURE

The FPT did not set the endpoint for isolated hip fractures, but for non-vertebral bone fractures, including hip fractures. In the group that received 20 µg of TPTD, there was only one case of fragility hip fracture compared to four in the placebo group. The number of hip fractures was relatively small, and the maximum of 24-months treatment with TPTD limited the ability to show statistically significant differences in hip fracture incidence between groups in prospective individual clinical trials.

As mentioned previously, TPTD increased femoral neck BMD by 3.6% in the FPT and by 3.9% in the FACT study compared to placebo. Black et al.<sup>18</sup> reported that at 24 months, hip BMD changes accounted for a substantial proportion (44-67%) of treatment-related fracture risk reduction; further, increased BMD is a surrogate end-point for fracture outcomes in future randomized trials for new osteoporosis therapies. Many studies, similar to FPT, have reported the preventive effects of TPTD in non-vertebral fractures including hip fractures. Additionally, large meta-analyses that set hip fracture as the endpoint reported that TPTD had a preventive effect. Díez-Pérez et al.<sup>19</sup> conducted a meta-analysis of 23 randomized controlled trials, which included 8,644 people. The meta-analysis reported that TPTD was effective in reducing hip fractures by 56%. In another meta-analysis, Silverman et al.<sup>20</sup> assessed data pooled from four prospective, observational studies, which included the Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE, United States)<sup>21</sup>, European Forsteo Observational Study (EFOS)<sup>3</sup>, Extended Forsteo Observational Study (ExFOS, Europe)<sup>22</sup>, and the Japan Fracture Observational Study (JFOS)<sup>23</sup>. For the 8,828 patients analyzed, the rate of hip fracture decreased during the reference period (0-6 months) to 44.3% (>6 to 12 months), 47.7% (>12 to 18), and 85.2% (>18 months). These data suggest that TPTD has a preventive effect on hip fractures.

### MECHANICAL PROPERTIES OF PROXIMAL FEMORAL GEOMETRY

Anatomical adaptations of the proximal femoral structure are important to maintain higher bone strength because they predict fracture risk independent of bone mass. A long bone

is primarily loaded in bending. On the superior surface of the bone, forces that are tensile try to pull the bone apart; on the inferior surface, the forces are compressive. The magnitude of deflection of the bone in bending is decreased by increasing the cross-sectional moment of inertia (CSMI). CSMI is equal to  $\pi/4$  multiplied by the difference between the outer radius raised to the fourth power and the inner radius raised to the fourth power (Fig. 3A)<sup>24</sup>. Small increments in the outer radius have a greater effect on the CSMI than relatively large increments in the inner radius. In other words, as the mass is distributed progressively away from the central axis, the CSMI increases, and the ability of the bone to resist bending forces increases. This can also be observed in the age-related bone loss where the resistance to fracture by expanding the outer diameter increases, while BMD decreases<sup>25</sup>.

Increasing the outer diameter can increase the resistance to fracture to some extent, but if the thickness of the cortical bone becomes too thin, the strength of the bone decreases rapidly. This can be explained by the buckling ratio that is the ratio of the outer radius to the cortical thickness. Local buckling occurs on the compressive surface when the buckling ratio is >10 (Fig. 3B)<sup>24</sup>. Therefore, both increases in the outer diameter and the thickness of the cortical bone are responsible for increased bone strength in long bones.

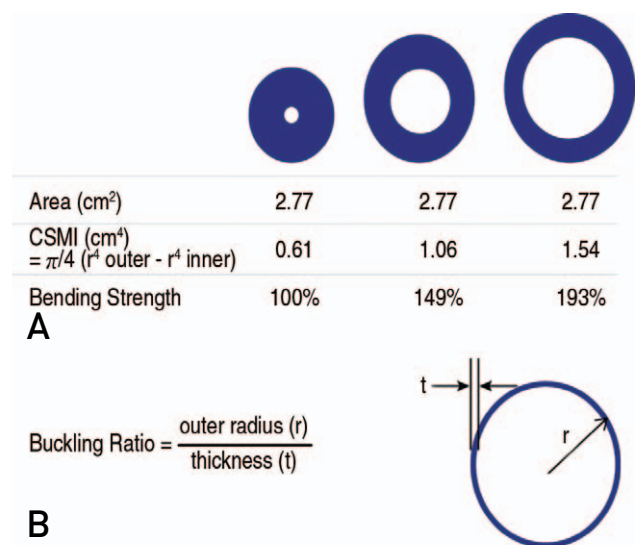


Fig. 3. (A) Although density decreased, the same section modulus is obtained by diameter expansion. (B) Buckling is the sudden change in shape (deformation) of a structural component under load. Local buckling begins to occur with a buckling ratio >10.

## INCREASE IN THE POROSITY, THICKNESS, AND OUTER DIAMETER OF CORTICAL BONE

TPTD increases intracortical porosity with bone remodeling, but increased porosity does not have a significant detrimental effect on the mechanical properties of the bone<sup>26</sup>. There are two reasons for this; first, most of the porosity is concentrated near the endocortical surface of the cross-section where the mechanical effect is small, second, porosity is accompanied by the apposition of new bone, both periosteally, and MBF and oMBF in the intracortical compartment. This results in an increased cortical thickness and diameter, and thus a CSMI.

### 1. Increase in Outer Diameter and Cortical Thickness

TPTD increases the outer diameter and cortical thickness through MBF and oMBF. The outer diameter is increased by MBF on the surface of the quiescent periosteum. In the iliac crest biopsy of 25 people who participated in the FPT, it was found that TPTD increases bone formation not only by MBF but also by oMBF (remodeling) in the cancellous bone<sup>10,27,28</sup>. Such oMBF occurs when there is an overabundant bone formation in the resorbed cavity and eventually on the quiescent surface site around the resorbed cavity (Fig. 2)<sup>10</sup>. Ma et al.<sup>29</sup> similarly reported that TPTD increased cortical thickness with oMBF in the cortical bone.

### 2. Increase in Cortical Porosity

Bone loss from bone remodeling occurs as a result of the negative balance between bone formation and resorption. In persons over 70 years of age, bone resorption from the cortex increases rapidly, as does the incidence of fragile hip fractures. Therefore, the effect of osteoporosis drugs on cortical porosity is key in preventing fragile hip fracture<sup>30</sup>. The use of PTH as an anabolic agent in osteoporosis raised concerns about the decrease in strength of the cortical bone, even with the potential of PTH to increase bone mass.

The effects of PTH on the skeleton could be either catabolic or anabolic depending on whether its levels are elevated chronically or intermittently. Primary hyperparathyroidism, a state of chronic increase in circulating PTH levels, is characterized by an increase in bone remodeling in favor of bone resorption and increased risk of fractures at all skeletal sites<sup>31,32</sup>. Some research has shown that patients who take PTH intermittently experienced a rise in bone remodeling and bone loss in peripheral bone, causing an

event termed the “cortical steal phenomenon”<sup>33,34</sup>. In the FPT, BMD of the lumbar spine and proximal femur increased, though BMD of the distal radius decreased compared to pre-treatment measurements, raising concerns about the decrease in the bone strength of the peripheral bone<sup>9</sup>. However, many results have been reported that PTH increases cortical bone porosity but does not decrease the strength of bone. Burr et al.<sup>26</sup> reported that the porosity of the cortical bone in the humerus increased in a dose-dependent manner when PTH was intermittently administered to cynomolgus monkeys, but most of the porosity was observed in the endocortex. Therefore, the effect on overall bone strength was insignificant and was offset by the increase in strength resulting from periosteal bone formation. Sato et al.<sup>35</sup> intermittently administered 1  $\mu\text{g}/\text{kg}$  (PTH1) and 5  $\mu\text{g}/\text{kg}$  (PTH5) PTH. The porosity increased by 27% in PTH1 and 33% in PTH5 compared to the ovarian resected group. However, the cortical thickness, width, and strength increased with the dose of PTH. Hansen et al.<sup>36</sup> reported that in a prospective study of postmenopausal osteoporosis patients, after 18 months of TPTD administration cortical bone porosity increased to  $32 \pm 37\%$  ( $P < 0.01$ ), and BMD decreased in the distal radius. However, the cortical thickness increased by  $2.0 \pm 3.8\%$  ( $P < 0.05$ ), and there was no change in bone strength. Osima et al.<sup>37</sup> reported that serum level of PTH is associated with increased cortical porosity of the inner transitional zone at the proximal femur in postmenopausal women, but cortical porosity was not related to the fractures. In summary, after the administration of TPTD, the porosity of the cortical bone increases, and the bone strength of the femur is maintained or increased.

## EFFECTS ON FRACTURE HEALING AND PERIPROSTHETIC BMD AROUND THE FEMORAL STEM

Although the exact mechanism by which intermittent injection of PTH stimulates bone union is unknown, it is clear that PTH acts upon the multiple steps of fracture healing<sup>38</sup>. PTH stimulates the formation of a soft callus by increasing the differentiation and proliferation of chondrocytes and the formation of cartilage. The next step is to stimulate the proliferation of osteoblastic progenitor cells and the proliferation of the bone matrix to increase the formation of hard callus. In the subsequent steps, PTH increases osteoclastogenesis and affects the hard callus to mature lamellar bone.

Manabe et al.<sup>39</sup> conducted a study on cynomolgus mon-

keys as they have a fracture-healing process similar to that of humans. Their results demonstrated that intermittent systemic administration of hPTH (1-34) accelerates the natural fracture healing process. This acceleration was featured by decreasing the size and porosity of the periosteal callus and increasing the degree of mineralization in the callus compared to the control, leading to significant increases in intrinsic material properties of the fractured femur shaft. In human studies, the fracture-healing effect of TPTD have been reported mainly as case reports<sup>40-43</sup>. In the clinical trial, Aspenberg et al.<sup>44</sup> reported that the group that was treated with 20 µg of TPTD showed a faster distal radial fracture union of an average of 7.4 weeks compared to 9.4 weeks in the control group ( $P=0.006$ ).

Several studies have demonstrated the loss of BMD around femoral implants, which is particularly a risk in the proximal part of the femur due to stress shielding around the implant<sup>45</sup>. Osteoblast activity may play an important role in the osteointegration between bone and implant. Bloebaum et al.<sup>46</sup> investigated the dynamics of osteoblast populations at the interface of porous-coated implants in an animal model, demonstrating that osteoblast activity is significantly greater in the porous-coated region than in the other non-porous-coated bone region. Bisphosphonates are known to be effective in reducing BMD loss around the femoral implant, but there is a concern for the long-term use of bisphosphonate<sup>47,48</sup>. TPTD may be advantageous for efficient osteointegration because of its ability to activate osteoblasts. Kobayashi et al.<sup>49</sup> reported that in a study comparing the changes in BMD around the femoral stem after administration of either TPTD or alendronate, the decrease in BMD around the femoral implant after surgery was not different from that of the group treated with alendronate. However, compared with the untreated group, TPTD did decrease the risk of BMD loss around the implant.

## EFFECTS ON HEALING OF ATYPICAL FEMORAL FRACTURE (AFF)

The subtrochanter is a common site where AFF occurs<sup>50</sup>. If the long-term use of bisphosphonates is associated with an AFF, the bisphosphonate should be discontinued first. If there is a complete fracture or pain with a dreaded black line on radiographic images, surgical treatment is recommended<sup>51-53</sup>.

There have been case reports of improved healing after using TPTD for AFF<sup>54-56</sup>. However, since the incidence of AFF is not high enough to generate statistical power in

prospective studies, meta-analysis or retrospective studies have typically been conducted. Shin et al.<sup>57</sup> reported that TPTD reduced the bone union time, with an average of 18 weeks in the TPTD group compared with that of 23 weeks in the non-TPTD group ( $P=0.001$ ). In a retrospective study, Yeh et al.<sup>58</sup> reported that TPTD treatment in patients with AFF may aid fracture healing. The average time for bone union was 4.4 months in the TPTD group (8 cases) compared with that of 6.2 months in the non-TPTD group (8 cases) ( $P=0.116$ ). Miyakoshi et al.<sup>59</sup> retrospectively reviewed the medical records of 45 consecutive AFFs in 34 Japanese patients who received oral bisphosphonates. The average fracture union time was significantly better in the TPTD group ( $5.4 \pm 1.5$  months) than in the non-TPTD group ( $8.6 \pm 4.7$  months;  $P=0.012$ ), and the frequency of delayed healing or non-union was significantly lower in the TPTD group than in the non-TPTD group ( $P=0.014$ ). In a prospective study without a controlled group was performed by Watts et al.<sup>60</sup> at 24 months fractures were healed completely in six patients, partially healed in three, unchanged in two, and showed non-union in one patient. In a patient with two fractures, the fracture that occurred before TPTD treatment was reported as healed, but the fracture that occurred while on treatment showed only partial healing. Watts et al.<sup>60</sup> suggested that TPTD should not be relied on to aid in the healing of the AFF. In a study examining the relationship between the commencement of administration of TPTD and the bone union effect Greenspan et al.<sup>61</sup> reported that six patients administered TPTD within six months (immediate group) of fracture showed greater bone union effect relative to those receiving TPTD between six and 12 months (delayed group) after a fracture. At 12 months, cortical continuity was 4.0 vs 3.6 (immediate and delayed, respectively;  $P=0.1032$ ), and composite scores were 15.4 vs 13.2 (immediate and delayed, respectively;  $P=0.1456$ ). Most studies showed a positive effect of TPTD on the healing of AFF therefore it is advisable to use TPTD taking into account its benefits and risks.

## SUMMARY

In addition to observing positive effects of TPTD on hip BMD and preventive effect on non-vertebral fractures, large meta-analyses indicate that TPTD prevents hip fractures. While TPTD increases porosity, it increases outer diameter and thickness of the cortical bone thereby increasing bone strength. TPTD has been shown to improve fracture healing in animal studies, case reports, and clinical trials, and

reduced BMD loss around the cementless femoral stem. Finally, while there is no conclusive evidence, TPTD is also recommended for AFF taking into account its benefits and risks.

## CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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