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Anabolic agents: what is beyond osteoporosis?

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Abstract

Osteoporosis is a common skeletal disorder characterized by low bone mass, which leads to reduced bone strength and an increased risk of fractures. Anabolic agents have been shown to improve bone mass and decrease fracture risk in osteoporosis patients by directly stimulating osteoblasts to produce new bone. Currently, two anabolic agents are available in the United States: recombinantly produced teriparatide (TPTD), which is the fully active (1–34) amino active sequence of human Parathyroid Hormone (PTH), and abaloparatide (APTD), a synthetic analog of Parathyroid Hormone-related Peptide (PTHrP). At present, both agents are approved only for treatment of patients with osteoporosis at high risk of fracture. Nonetheless, their anabolic properties have led to off-label application in additional settings which include spine fusion, osteonecrosis of the jaw, arthroplasty, and fracture healing. In this article we summarize available scientific literature regarding the efficacy, effectiveness, and safety of TPTD in these off-label settings.

Keywords

Osteoporosis; anabolic agent; teriparatide; fracture

Introduction

Osteoporosis is a common skeletal disorder characterized by low bone mass, which leads to reduced bone strength and an increased risk of fractures [1]. It is estimated that osteoporosis affects about 200 million individuals worldwide [2]. The pharmacologic treatment of osteoporosis includes anti-resorptive agents and anabolic agents [1]. Anti-resorptive agents, such as bisphosphonates, denosumab, and selective estrogen modulators, do not enhance new bone formation, but rather limit osteoclast function, resulting in a decreased rate of bone turnover, decreased bone resorption, and subsequent improvement of bone mineral density (BMD) [1]. Anabolic agents, on the other hand, directly stimulate osteoblasts to improve bone mass and volume as well as decrease fracture risk [1].

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Teriparatide (TPTD), a human recombinant parathyroid hormone (PTH), was the first anabolic agent in the United States to treat osteoporosis [1]. The actual indications for TPTD includes postmenopausal osteoporosis, glucocorticoid induced osteoporosis and male osteoporosis. Abaloparatide, a synthetic analog of a parathyroid hormone-related peptide (PTHrP), was recently approved for osteoporosis by the United States Food and Drug Administration (FDA) in April 2017 [3]. Previous studies have shown TPTD is superior to anti-resorptive agents with regards to increasing BMD and lowering fracture risk [4]. In addition, anabolic agents, particularly TPTD, are commonly used off-label in other orthopedic settings including spine fusion, stress fracture, fracture healing, and arthroplasty. The therapeutic effect is thought to derive from the drug's anabolic effect on bone.

In this article, we summarize the available evidence in the literature regarding the safety and efficacy of off-label treatment with anabolic agents in the setting of spine fusion, osteonecrosis of jaw, arthroplasty, and fracture healing.

Anabolic agents: mechanism

Intermittent administration of both PTH and PTHrP analogs in the form of once daily subcutaneous injections has previously been shown to stimulate bone formation more than resorption and subsequently reduce the incidence of fractures. In contrast, continuous administration of PTH and PTHrP analogs results in bone resorption [5]. TPTD is a recombinant protein containing the first 34 amino acids in the peptide (PTH 1–34). The truncated recombinant molecule shares the biological activities of the full 84 amino acid PTH. Both PTH and PTHrP binds to PTH type 1 receptor (PTHR1), a G-protein coupled receptor that has two different high affinity confirmations R^0 and RG. Abaloparatide is a synthetic analog of PTHrP 1–34 that has a higher selectivity to the RG confirmation of PTHR1 compared to TPTD [6]. Such difference confers a more transient response to ligand binding and lowers the incidence of hypercalcemia with abaloparatide use compared to TPTD in clinical trials [7]. Currently, abaloparatide is only approved to treat postmenopausal osteoporosis, and there is no published data on off-label use of abaloparatide [7].

Another anabolic agent that has been investigated is Romosozumab – a sclerostin antibody. Sclerostin is an inhibitor of the Wnt signaling pathway, which plays an important role in osteoblast differentiation and bone remodeling. Romosozumab is a humanized monoclonal antibody that binds to sclerostin, preventing sclerostin from exerting its inhibitory effect [8]. Though romosozumab shows promising effect in improving BMD and decreasing fracture risk, a phase III clinical trial demonstrated an unexpected higher incidence of cardiovascular events compared with patients treated with alendronate group. The drug was therefore not approved by the FDA [9]. Given the limited clinical data available on abaloparatide and romosozumab, this review article will mainly focus on the off-label use of TPTD.

Spine fusion

Spinal fusion involving lumbar instrumentation is a common method to provide spine stability in patients with degenerative lumbar spine disease or spinal deformity. However, low bone mass or poor quality of the underlying bone in these patients may increase the risk

of surgical complications, such as hardware loosening, pseudoarthrodesis, and the need for revision surgery [10].

At present, most preclinical studies have demonstrated the efficacy of TPTD for improving lumbar arthrodesis fusion rates in both rat and rabbit animal models (Table 1). In a study of 56 rats with single-level spinal fusion, the TPTD group showed a trend towards greater fusion rate as compared to controls [11]. Similarly, another study found that the fusion rate was significantly higher in the TPTD group (TPTD 40μg/kg/day) than the 0.9% saline placebo group at 14 days (57% vs. 14%). In addition, TPTD accelerated grafted bone resorption (a factor essential for bone remodeling and ultimate healing), and produced a larger and denser fusion mass compared to the control group [12]. In another study, L4-L5 fusion rates were significantly higher in the TPTD group (30μg/kg/day) compared to a control group at 4 week and 6 week follow up [13]. Furthermore, TPTD dosed at 40μg/kg/day has been shown to increase fusion rate in rats with glucocorticoid-induced osteoporosis [14]. Ming et al. further investigated this effect, by comparing spine fusion in high (23μg/kg/day) and low (4μg/kg/day) dose regimens. The high dose group experienced a significant enhancement in fusion rate whereas the low dose group did not show significant improvement in radiology scores compared with the control group [15]. Regarding combination therapy with bisphosphonates, an ovariectomized rat model of osteopenia showed both TPTD combined with zoledronic acid and TPTD monotherapy increased the bone fusion rate, while zoledronic acid monotherapy did not change the fusion rate [16]. Two studies have also demonstrated a beneficial effect of TPTD on spine fusion rates in healthy rabbit models [17, 18]. Histologically, many of these animal studies have shown that TPTD induced bone formation by stimulating osteoblasts and osteoclasts [12, 13, 17]. This is further supported by the presence of higher levels of bone turnover markers in the TPTD-treated animals [11, 13]. The spine fusion callus proceeded through enhanced endochondral bone formation only in the TPTD treated rabbits [17].

Several clinical studies have confirmed the effectiveness of TPTD in patients undergoing lumbar spine fusion (Table 2). TPTD is superior with regards to fusion rate and resulted in earlier bone fusion compared with placebo or oral bisphosphonates in many retrospective analyses [19–22]. Most of the studies were initially retrospective, but recently controlled prospective studies also have been reported. A recent prospective randomized clinical trial compared spine arthrodesis fusion rates in women with single level posterior or transforaminal lumbar interbody fusion. Of 66 patients who completed the study, 29 patients received weekly TPTD (administered subcutaneously starting at week 1 for a 6-month period), while 37 participants were assigned to the no treatment control group. At 4 months and 6 months postoperative follow up periods, the TPTD group had a significantly higher fusion rate than the control group (69.0% versus 35.1%)[23].

There were three prospective studies comparing TPTD versus oral bisphosphonates in patients undergoing spine fusion surgeries. In a group of fifty-seven osteoporotic women who underwent posterolateral fusion without interbody fusion, daily TPTD injection for 10 months was more effective in achieving bony union than oral bisphosphonates for 10 months (82% versus 68% respectively). Time to radiographic fusion was 8 months in the TPTD group and 10 months in the bisphosphonate group [24].

In another prospective study, Seki et al. investigated two year outcomes of spine fusion in 58 osteoporotic Japanese female patients. Patients received either TPTD (33 patients) or oral alendronate (25 patients) and each drug was administered for 3 months before and 21 months after surgery. At 2 year follow-up, adjacent vertebral fractures, implant failure, arthrodesis non-union, and poor pain control were significantly more prevalent in the bisphosphonate group than the TPTD group [25].

In a prospective study, 47 osteoporotic patients who underwent posterior lumbar interbody fusion were divided into two groups, receiving either daily TPTD 20 μg subcutaneous injections for 3-month cycles alternating with 3-month periods of oral alendronate(n=23) or oral alendronate for 12 months (n=24). The TPTD group showed earlier fusion than the bisphosphonate group, with radiographically confirmed fusion present at an average of 6.0 ± 4.8 months in the TPTD group and 10.4 ± 7.2 months in the alendronate group. The fusion rate in the TPTD group was higher than that in the bisphosphonate group at 6 months (77.8% versus 53.6%); however, there was no difference at 12 and 24 months after surgery [26]. The higher fusion rate observed with TPTD versus bisphosphonate treatment can likely be attributed to TPTD's positive effect on bone microarchitecture [27].

Finally, in addition to more successful and earlier bone union, previous studies have also shown that TPTD has beneficial effects on maximizing the purchase of pedicle screws [22]. In 29 osteoporotic patients who underwent thoracic and/or lumbar spine fusion, one group received preoperative TPTD therapy for at least 1 month and the second group did not receive preoperative treatment. During surgery, the mean insertional torque measurements from T-7 to L-5 in the group receiving TPTD pre-treatment was significantly higher than in the control group (1.28 ± 0.42 Nm in TPTD group versus 1.08 ± 0.52 Nm in control group) [22]. This was corroborated by two additional studies finding a lower incidence of screw loosening in patients receiving TPTD treatment than control group who did not take TPTD [19, 28].

In terms of the most effective duration of TPTD use, Ohtori retrospectively looked at 45 osteoporotic patients after posterior lumbar interbody fusion. Fifteen patients were classified as short-duration TPTD treatment (average 5.5 months) and fifteen were regarded as long-duration TPTD treatment (average 13.0 months). Both fusion rate and average time to fusion were significantly superior in the long-duration treatment group when compared with short-duration treatment group (92% and 7.5 months versus 80% and 8.5 months respectively) [20]. Subsequently, these authors sought to determine whether discontinuing TPTD treatment and replacing it with bisphosphonate treatment would maintain the volume of the fusion mass [21]. They demonstrated that after perioperative TPTD was discontinued, bisphosphonate therapy maintained bony fusion masses with fusion rate remaining at 95% at 2 and 3 year follow up periods [21].One of the theoretical safety concerns of TPTD is that use of TPTD could exacerbate spinal stenosis, particularly in patients who are candidates for spinal fusion. However, in a recent prospective study, investigators did not find evidence of increased risk of spinal narrowing on CT after 2 years of TPTD treatment [29].

Based on the combined animal and clinical trials, TPTD as compared to controls and bisphosphonates demonstrates efficacy in enhancing spine fusion, diminishes instrument

displacement, and facilitates functional recovery. Currently NIH is supporting a randomized trial that directly examining TPTD in spine fusion (NCT01292252).

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) after dental extraction is a rare complication in patients with long term bisphosphonates or denosumab use. TPTD has been used to treat ONJ in animal studies and several clinical case reports. Keskinruzgar et al. showed that in rats receiving zoledronic acid prior to tooth extraction, those who received TPTD before and immediately after tooth extraction had larger osteoclasts and a more pronounced inflammatory phase of bone healing compared with rats that received zoledronic acid only [30]. However, once ONJ developed, TPTD did not show any beneficial effect. Additionally, there was no difference in osteoblast numbers and osteonecrotic areas between the TPTD and control groups [30]. In contrast, researchers using another rat model found that adjunctive TPTD administration after tooth extraction lowered the incidence of ONJ. They also noticed that the presence and severity of inflammation was lower (77.7% in the TPTD group versus 100% in the control group), though their study was underpowered to show a statistically significant difference [31].

Several case reports have demonstrated successful treatment of TPTD in bisphosphonate-related ONJ [32, 33]. In a recent study that involved 17 patients undergoing sequestrectomy, combination treatment with TPTD and bone morphogenetic protein (BMP) significantly enhanced bone formation and promoted bone regeneration compared to both patients receiving BMP monotherapy and a surgery-only control group [34]. In patients with stage 3 bisphosphonate-related ONJ refractory to conservative management, weekly TPTD administration was as effective as daily TPTD in promoting bone healing and removing osteonecrotic tissue [35]. Kim et al. conducted a retrospective study in patients with ONJ and found that the TPTD group showed better resolution of ONJ compared with patients in the comparison group [36]. Similarly, a randomized, placebo-controlled, double-blind trial demonstrated that TPTD was associated with improved clinical outcome, greater resolution of alveolar bone defects as well as accelerated wound healing in patients with severe chronic periodontitis [37].

Of note, the incidence of ONJ is much higher in oncology patients who receive more intensive anti-resorptive medication regimens than those with osteoporosis [38]. However, previous animal studies have shown that rats treated with higher doses of TPTD have an increased risk of developing osteosarcoma; therefore, TPTD is not recommended in patients with active cancer or with a history of radiation therapy [39]. Further prospective, randomized studies are needed to better delineate the safety and efficacy of TPTD in the setting of ONJ. At this time, it is too early to strongly support the use of TPTD for preventing and resolving ONJ. However, in the setting of patients scheduled for dental implants and low bone density, anabolic agents have demonstrated efficacy changing the bone metabolic environment favorably.

Arthroplasty

There are several animal and clinical studies on the use of TPTD in total joint arthroplasty; however, the results remain controversial. In rat and canine models, the administration of TPTD had a positive effect on implant fixation [40, 41]. Such an effect is not blunted by anti-resorptive agents, as rats receiving TPTD/zoledronic acid showed significantly stronger effects than zoledronic acid alone on histological, micro-CT, and biomechanical testing [41]. Three case reports described improvement of implant stability in patients with loosening prostheses after receiving treatment with TPTD [42–44]. In a retrospective study, patients with weekly injection of TPTD after cementless total knee arthroplasty found that TPTD promoted bony ingrowth; however, this enhanced ingrowth was limited to the medial aspect of the bone-prosthesis interface [45]. Another retrospective study of patients who received cementless hemiarthroplasty for femoral neck fractures revealed a significant reduction in the rate of femoral stem subsidence in patients treated with TPTD at 6 weeks and 12 weeks post-operatively. However, TPTD did not improve clinical outcomes, quality of life scores, subsequent fracture risk, or mortality in these patients [46]. In a randomized prospective study, daily TPTD injections for 48 weeks did not show superiority over weekly alendronate in preserving the periprosthetic BMD, despite resulting in improved lumbar spine bone mineral density and bone turnover markers [47]. In another randomized clinical trial, implant migration (as indicated by median maximal total point motion after total knee arthroplasty) was similar in the TPTD group compared to the untreated control group in 24 months follow up [48]. However, in those cases of microfracture and stress reaction following porous implant insertion, there may be some value (see below) for anabolic agents.

Fracture healing

The use of TPTD also has theoretical benefits with regards to the various phases of fracture healing. Secondary, or indirect, fracture healing is the most common type of fracture healing and is comprised of several stages: inflammation, callus formation, and remodeling. The initial inflammatory phase occurs rapidly with hematoma formation at the fracture site and a powerful cytokine inflammatory response. Within 2–3 weeks of the acute injury, progenitor cells from the periosteum and endosteum are stimulated to become osteoblasts, initiating a process of endochondral bone formation that ultimately creates a cartilaginous callus. Subsequently, this endochondral callus mineralizes and disorganized woven bone undergoes structural remodeling via surface erosion and osteonal remodeling to become lamellar bone [49]. TPTD has been shown to enhance early and late endochondral bone formation through its effects on the Wnt signaling pathway [48]. PTH-rP is involved in early regulation of chondrogenesis, slowing differentiation to allow for proliferation of chondrocytes in the endochondral bone formation process. Additionally, TPTD administration has been shown in rat fracture models to result in increased overall fracture callus size via the proposed mechanism of a relative increase in chondrogenic versus osteogenic responses [50].

Preclinical studies have demonstrated the efficacy of TPTD in various models of fracture healing [51–53]. Rat femoral fracture models treated with daily 10 μg/kg subcutaneous TPTD injections showed significant increases in numbers of osteoprogenitor and tartrate-

resistant acid phosphatase (TRAP) positive cells, type 1 collagen messenger RNA production, osteonectin, alkaline phosphatase, and osteocalcin, all correlating with significantly increased callus bone mineral content and BMD versus placebo [54]. These results suggest that TPTD enhances osteoclastogenesis and the production of bone matrix proteins, theoretically contributing to fracture healing during the callus remodeling phase. Additional preclinical fracture models demonstrated significantly improved mechanical properties of bony callus (including ultimate load and torsional strength), external volume, bone mineral content, and BMD with TPTD treatment ranging from 0.75–200 μg/kg/d [51–53]. Furthermore, adding TPTD to recombinant human bone morphogenic protein 7 (rhBMP-7) [55], mesenchymal stem cell [56], and zoledronic acid [57] treatments improved fracture healing outcomes compared to treatment without TPTD in preclinical models. However, TPTD did not significantly increase the rate of union in an open fracture model in rat femurs compared to placebo, suggesting TPTD treatment is more effective in closed versus open fractures [58]. Additionally, rats treated with PTH 1–34 14 days post-osteotomy showed no increase in callus BMD and less pronounced enlargement in callus area compared to rats beginning treatment 7 days post-osteotomy, suggesting that early TPTD treatment provides greater fracture healing benefit [59]. Parathyroid hormone or parathyroid hormone-related protein (PTHrP) analogs have also shown efficacy in treating animal models of non-union [60] and stress fracture [61]. Of note, the applicability of these findings to human subjects is questionable given that the dosages used in preclinical models exceed the recommended human doses for equivalent clinical conditions [27].

A limited number of clinical studies have also demonstrated a beneficial effect of TPTD on fracture healing. In a prospective randomized trial, 102 postmenopausal women with non-operatively treated extra-articular distal radius (Colles type) fractures were assigned to receive placebo, TPTD 20 μg/day, or TPTD 40 μg/day for 8 weeks. The median time to fracture healing was significantly shorter in the TPTD 20μg/day group (7.4 weeks), but not in the TPTD 40 μg/day group (8.8 weeks) compared with the placebo group (9.1 weeks) [62]. These investigators conducted a second analysis evaluating the qualitative appearance of callus with respect to these various TPTD doses. In contrast to the lack of dose effect in their initial study, this second analysis revealed a dose-dependent beneficial effect of TPTD on qualitative callus appearance [63]. Despite previous studies that showed decreased bone density in distal radius with TPTD treatment, Aspenberg et al. proved that TPTD was associated with enhanced fracture healing [62]. The explanation for this may be that DXA only measures areal BMD and may not reflect bone strength. In addition, a previous study demonstrated that TPTD induced beneficial changes in bone microstructure of the distal radius consistent with increased mechanical strength [27].

Likewise, Peichl et al. performed a prospective study in elderly osteoporotic patients with pelvic fractures. Patients treated with a once daily injection of recombinant PTH 1–84 at a dose of 100 μg/day had an average fracture-healing time of 7.8 weeks, compared with 12.6 weeks in the control group [64]. A prospective, randomized clinical trial (NCT02972424) is now being conducted to investigate the effect of TPTD in osteoporotic patients with acute low energy pelvic fracture.

Atypical femoral fractures (AFFs) occur in the subtrochanteric or diaphyseal regions of the femur after a low impact injury, most commonly after prolonged anti-resorptive medication (bisphosphonate or denosumab) use. This is thought to occur as a result of over-suppression of the bone remodeling process [65]. TPTD has been used off-label clinically to treat AFF in case reports and case series [66–70]. One retrospective study of 37 surgically treated AFF patients found that the average time to AFF healing was significantly shorter in patients treated with TPTD (5.4 ± 1.5 months) compared to patients who did not receive this medication (8.6 ± 4.7 months). Furthermore, the rates of delayed union and non-union were also lower in the group treated with TPTD. However, a subanalysis of conservatively treated incomplete AFFs revealed no differences between groups [71]. The author attributes the discrepancy to the relative small sample size in conservatively treated AFF patients. A small non-randomized prospective study in 14 patients who developed AFF after chronic use of bisphosphonates revealed that after TPTD treatment for 6 months (n=5) resulted in a significant increase in bone turnover markers (C-telopeptide and procollagen Type 1 N-terminal propeptide) compared to patients not treated with TPTD (n=9). In patients treated with TPTD, high resolution peripheral micro-computed tomography scans of the distal radius and distal tibia obtained at baseline and 6 months after AFF fixation found that TPTD helped to remove old fully mineralized bone matrix, and replaced it with less fully mineralized bone matrix, therefore restoring the heterogeneity in tissue mineralization density [72]. This finding is of great importance, as bisphosphonates increase bone matrix stiffness and reduce bone ductility, making bone more brittle and, therefore, increasing the risk of AFF [73, 74]. This is further confirmed by Miller et al., who conducted a similar study in 15 AFF patients comparing iliac crest biopsy histomorphometry before and after TPTD treatment (20 μg/day). Administration of TPTD was associated with an increase in bone formation, bone surface area undergoing mineralization, and mineral apposition [75]. However, a recent two-year prospective open-label study by the same investigators showed that while TPTD 20ug/day improved bone turnover marker levels and lumbar spine BMD, it had minimal effect on hip bone density or the percent of bone surface undergoing active mineralization [68]. This study was unable to adequately evaluate AFF healing due to small sample size and lack of a control group [68]

The evidence regarding the use of TPTD in fractures complicated by delayed union and non-union is limited to anecdotal reports. One such case report documented successful treatment of a peri-prosthetic humeral diaphysis non-union using internal fixation, augmented with massive bony autograft and post-operative treatment with 3 months of TPTD at a dose of 20 μg/day [76]. Similar reports have been published in other settings including, tibia/fibular, femur, ulna and type II odontoid fracture non-unions [69, 70, 77]. Given the lack of controlled studies, conclusions with respect to the effect of TPTD on fracture healing in non-unions are only speculative.

Finally, stress fractures often prove to be challenging fractures to heal [78]. These overuse bony injuries are caused by repetitive physiologic stresses and are commonly seen in athletes [78]. Current studies of TPTD and stress fracture are limited to case reports. Raghavan et al. reported that TPTD alleviated pain and led to successful fracture healing in two patients with metatarsal stress fractures [79]. Stress fractures are also a common manifestation in adult hypophosphatasia [80]. Whyte et al. reported TPTD promoted fracture healing, relieved

bone pain and corrected hypophosphatasemia in an adult patient with hypophosphatasia [80].

At this time, the randomized studies by Aspenberg and Peichl et al, demonstrated significant enhancement for fracture repair in low energy fragility fractures. In addition to the randomized studies in fragility fractures, there are anecdotal reports of the beneficial effects of TPTD in atypical femoral fractures, delayed or non-union in all forms of fractures as well as stress fractures. The other applications need further well-performed studies to confirm TPTD's efficacy.

Conclusion

In conclusion, studies have demonstrated that intermittent TPTD injection has clinical benefits in the setting of spine fusion, but remains controversial with regards to use in arthroplasty, osteonecrosis of the jaw, and fragility fracture healing. Although most current clinical series on ONJ, acute fractures and delayed union demonstrate a positive effect, data for these indications remains limited. Theoretically, TPTD may improve bone microstructure and serve as a potential adjuvant treatment for atypical femur fractures and stress fractures; however, concrete evidence is lacking in these patients presently. Further adequately powered, prospective, controlled studies are warranted to substantiate the use of TPTD in these controversial areas. Similarly, additional studies are needed to substantiate the role of other anabolic agents such as abaloparatide for these off-label indications. Based on a large array of literature, patients with osteoporosis requiring bone intervention (fractures, spine fusion) and evidencing inadequate fixation and compromised bone quality would benefit from an anabolic agent over the use of anti-resorptive agent.

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Table 1

Pre-clinical studies of Anabolic agent effects

Clinical Conditions	Animal Model	Groups	Results	Reference
Spine Fusion	Rat	Control; ZA; TPTD 60 μg/kg/2d; ZA + TPTD 60 μg/kg/2d	ZA and TPTD monotherapy increased bone volume at fusion site, and ZA+TPTD combined therapy had an additive effect vs control TPTD and ZA+TPTD increased bone fusion rate vs control group	Yishake 2017 [16]
	Rat	TPTD 40 μg/kg/day 5 times a week for 6 weeks postoperative; Control	Fusion mass volume significantly greater in TPTD group Fusion rate significantly higher in TPTD group than control group (89% vs. 56%)	Sugiura 2015 [14]
	Rabbit	Autograft; Autograft + TPTD 10μg/kg/day; Low dose rhBMP-2; Low dose rhBMP-2+ TPTD 10μg/kg/day High dose rhBMP-2; High dose rhBMP-2+ TPTD 10μg/kg/day	CT radiographs revealed unilateral or bilateral fusion in 50% of spines in the autograft control group, 75% of spines in the TPTD- treated group, 87.5% in both low-dose rhBMP-2–treated groups, and 100% in both high-dose rhBMP-2–treated groups	Lina 2014 [81]
	Rat	TPTD 30 μg/kg/day; control	Significantly higher fusion rate in TPTD group vs control group at 4 weeks (55.6% vs. 22.2%) and 6 weeks (88.9% vs. 55.6%) Significantly higher average radiologic score in TPTD group at 4 weeks (2.03 vs. 1.45) and 6 weeks (3.66 vs. 2.56)	Qiu 2013 [13]
	Rat	TPTD (low dose) 4 μg/kg/day 5 days/week for 4 weeks post-op; TPTD (high dose) 23 μg/kd/day 5 days/week for 4 weeks post- op; Vehicle	Fusion rates significantly higher in high dose (68%), low dose (50%) groups than control group (20%) in a dose-dependent manner by manual palpation Radiologic and micro-CT scores significantly higher in high dose and low dose groups in a dose-dependent manner	Ming 2012 [15]
	Rabbit	TPTD 10 μg/kg/day 8 weeks post-op; Control 14 IU/animal calcitonin 8 weeks post-op	Histologic fusion rates significantly higher in TPTD group (86.7% vs. 50%) Trend toward radiographic superiority in TPTD group (85.7% vs. 56.3%)	Lehman 2010 [18]

Clinical Conditions	Animal Model	Groups	Results	Reference
	Rabbit	TPTD 10 μg/kg/day; Control	Fusion rate significantly higher in TPTD group than control group (81% vs. 30%) Compared with control group, TPTD resulted in higher radiographic scores (4.51 vs. 3.36) and higher median mass (6.03ml vs. 3.5ml)	O'Loughlin 2009 [17]
	Rat	TPTD 40 μg/kg/day; Control	Fusion rate significantly higher in TPTD group than control group (57% vs. 14%) TPTD produced a larger and denser fusion mass compared to control	Abe 2007 [12]
	Rat	TPTD 10 μg/kg/day; Control	Fusion rate significantly higher in TPTD group than control group	Lawrence 2006 [11]
Osteonecrosis of Jaw (ONJ)	Rat	ZA + DM + 0.04 mg/kg TPTD 2x/week for 3 weeks prior to tooth extraction; ZA + DM + 0.04 mg/kg TPTD 2x/week for 3 weeks after tooth extraction; ZA + DM+ 0.04 mg/kg TPTD 2x/week for 3 weeks after ONJ onset; ZA + DM (control)	Pre-extraction and post-extraction TPTD groups had greater osteoclast number vs control (P = 0.037 and 0.079) Inflammatory phase of bone healing more pronounced in pre- extraction TPTD group vs control (P = 0.011) No significant differences in osteonecrotic area (P = 0.324) in experimental vs control groups	Keskinruzgar 2016 [30]
	Rat	**I.** 0.1 mg/kg sterile saline (SS) 3x/week for 8 weeks; **II.** 0.1 mg/kg zoledronic acid (ZA) 3x/week for 8 weeks; **III.** 0.1 mg/kg ZA 3x/week for 8 weeks + molar extraction; **IV.** 0.1 mg/kg ZA 3x/week for 8 weeks + molar extraction + TPTD 30 mg/kg/day for 8 weeks	0% ONJ observed in groups I and II; 66% ONJ in group III (P < 0.01) 22% ONJ in group IV; no significant difference vs groups I and II (P > 0.01) Less inflammation in group IV vs group III, although statistically insignificant (P > 0.01)	Dayisoylu 2013 [31]
Arthroplasty	Canine	Proximal tibia alloy implant + TPTD 5 μg/kg daily×1 month; Control	Bone contact non-significantly increased at implant interface in TPTD group (P = 0.07); Median shear stiffness significantly higher in TPTD group (P < 0.05)	Daugaard 2011 [40]
	Rat	Endosseous implant; Implant + TPTD 60 μg/kg, 3x/week×12 weeks; ZA coated implant;	TPTD+ZA treatment produced most significant increases in BV/TV, B.Ar/T.Ar, and BIC (p < 0.05) TPTD+ZA significantly increased maximal push-out	Li 2013 [41]

Clinical Conditions	Animal Model	Groups	Results	Reference
		ZA coated implant + TPTD 60 μg/kg, 3x/week×12 weeks	force, stiffness, and toughness ($p < 0.05$)	
Fracture healing	Rat	TPTD 10 μg/kg/day; Control	Bone mineral content, bone mineral density, and ultimate load to failure of fracture calluses were significantly increased in the TPTD- treated group compared with controls (day 28, 61, 46, and 32%; day 42, 119, 74, and 55%, respectively)	Nakajima 2002 [54]
	Rat	TPTD 60 μg/kg/day; TPTD 200 μg/kg/day; Control	200 μg dose increased external callus volume after 20 days (99%) and 40 days (72%) versus control 60 μg dose did not influence external callus volume after 20 days, but increased external callus volume (42%) after 40 days versus control	Andreassen 1999 [51]
	Rat	TPTD 5 μg/kg/day; TPTD 30 μg/kg/day; Control	TPTD 30 μg group had significantly increased torsional strength and bone mineral density in day 21, day 35 and day 84 TPTD 5 μg group was associated with increased torsional strength and bone mineral density in day 35	Alkhiary 2005 [52]
	Monkey	TPTD 0.75 μg/kg; (Low dose) TPTD 7.50 μg/kg; (High dose) Control	Ultimate stress test and elastic modulus significantly higher in TPTD-high dose versus control Callus porosity decreased dose-dependently following TPTD treatment. Mean DMB of callus was significantly higher in high dose (1.42 ± 0.30) than in control (1.09 ± 0.26) or low dose(1.13 ± 0.24)	Manabe 2007 [53]
	Rat	TPTD 50 mug/kg; Control Treatment 5 days per week	TPTD significantly increased callus bone mineral content and volume and trabecular bone volume/total volume (BV/TV) in open and closed fractures In closed fractures, TPTD significantly increased callus size, strength, and peak torque versus control TPTD did not significantly increase union rate in open fractures versus control	Tagil 2010 [58]
	Rabbit	200μg rhBMP-7; 200 μg rhBMP-7 + 10μg/kg/day TPTD; 10μg/kg/day TPTD	TPTD + rhBMP-7 showed greater woven trabecular bone quantities, increased trabecular thickness, decreased trabecular separation ($p < 0.04$), and a trend towards increased numbers of osteoclasts (p =	Morgan 2008 [55]

Clinical Conditions	Animal Model	Groups	Results	Reference
			0.09) ; increased torsional rigidity and compressive strength vs control and BMP-7 groups ($p < 0.001$)	
	Rat	4 μg/kg/day TPTD; Five injections of 2 × 106 human mesenchymal stem cell (hMSCs); 4 μg/kg/day TPTD+ five injections of 2 × 106 hMSCs	Significant increase in bone volume seen only in the TPTD + hMSC group 8 weeks post-surgery, higher rate of complete bone bridging in TPTD + hMSC group (35%) in compared to 6.25% in TPTD alone, and 0% in control and MSC groups	Cohn Yakubovich 2017 [56]
	Rat	1.5 μg/kg weekly ZA; TPTD 60 μg/kg, three times a week; 1.5 μg/kg weekly ZA+ TPTD 60 μg/kg, three times a week	ZA + TPTD showed strongest effects on BV/TV, trabecular thickness, total fluorescence-marked callus area, and biomechanical strength	Li 2012 [57]
	Rat	Healthy TPTD 40 μg/kg 5x/w 7-35d; OVX TPTD 40 μg/kg 5x/w 7-35d; OVX TPTD 40 μg/kg 5x/w 14-35d; OVX TPTD 40 μg/kg 5x/w 14-28d	No changes in biomechanical stiffness or yield load seen in TPTD treatments 14 days post-osteotomy versus untreated healthy or OVX rats In OVX rats treated with TPTD 14-28 days post-osteotomy, no increase in callus bone mineral density Less pronounced enlargement in callus area for OVX rats started on TPTD treatment 14 days post-osteotomy compared to those started at 7 days	Komrakova 2010 [59]
Non-union	Rat	PTH 1-34 30 μg/kg/day for 2 weeks; Control in surgical model of femoral non-union	PTH treated group showed greater rate of bony union (50% vs 8%; $P < 0.05$) and lower mean gap size (1.42 vs 0.36 mm; $P < 0.05$) at 6 weeks post-op versus control	Lin 2012 [60]
Stress fracture	Rat	TPTD 40 μg/kg; alendronate 2 μg/kg; Control	TPTD treatment group showed significantly increased bone formation (114%) at 2 weeks, increased intracortical resorption area (23%) at 4 weeks, and enhanced ultimate force (15%) at 8 weeks versus control	Sloan 2010 [61]

Abbreviations: TPTD: teriparatide; ZA: zoledronic acid; rhBMP: recombinant human bone morphogenetic protein; BMP-7: bone morphogenetic protein 7; DM: Dexamethasone; BIC: Bone to implant contact; ONJ: Osteonecrosis of jaw; SS: Sterile saline; OVX: Ovariectomized; hMSC: human mesenchymal stem cells; BV: bone volume; TV: total volume; AP: Anterior/Posterior; DMB: Degree of mineralization in bone; CT: Computed tomography; B.Ar: bone area; T.Ar: total area

Table 2

Clinical studies of teriparatide effects

Clinical Conditions	Patient Number	Study Type	Groups	Follow-up time	Results	Reference
Spine fusion	19	Retrospective	TPTD 20 μg daily, 2 months pre-op and 8 months post-op. After discontinue TPTD, 17.5 mg risedronate weekly	36 months	Bone union rate 95% at 2 year and 3 year follow up	Ohtori 2017 [21]
	62	Retrospective	TPTD 20 μg 7.4 months post-op; Control	12 months	Bone union rate 66.7% in the TPTD group and 50% patients in the control group. Incidence of screw loosening was lower in TPTD (13.4%) compared to 24.4% in the control group	Kaliya 2017 [19]
	45	Retrospective	TPTD 20 μg daily×5.5 months; TPTD 20 μg daily×13 months; BPs: risedronate 17.5 mg weekly × 3 months pre-op, 12 months post-op	15 months	Bone union rate were 92% in the long-duration TPTD group, 80 % in short-duration TPTD group and 70% in the BPs group. Average duration for bone union 7.5 months in the long- duration TPTD group, 8.5 months in the short-duration TPTD group and 10.0 months in the BPs group	Ohtori 2015 [20]
	62	Retrospective	TPTD 20 μg daily or TPTD 56.5 μg weekly×minimum 1 months pre-op; Control	N/A	The mean insertional torque value in the TPTD group was significantly higher than in the control group (1.28 ± 0.42 Nm versus 1.08 ± 0.52 Nm, $p < 0.01$). No significant difference between the daily and the weekly TPTD groups with respect to mean insertional torque value (1.34 ± 0.50 Nm and 1.18 ± 0.43 Nm, respectively, $p = 0.07$). There was negligible correlation between insertional torque and duration of preoperative TPTD treatment ($r2= 0.05$, $p < 0.01$)	Inoue 2014 [22]
	47	Prospective	TPTD 20 μg daily × 3months post-op cycling with alendronate 91.37 mg weekly × 3 months for 12 months; BPs: alendronate 91.37 mg weekly × 12 months	24 months	Time to fusion was 6.0 ± 4.8 months in the TPTD group and 10.4 ± 7.2 months in the BPs group. The bone fusion rate in the TPTD group was higher than that in the bisphosphonate group at 6 months but no difference at 12 and 24 months	Cho 2017 [26]
	66	Prospective	TPTD 56.5 μg weekly × 6 months post-op;	6 months	Bone fusion rate is higher in TPTD (69.0%) than control group (35.1%)	Ebata 2017 [23]

Clinical Conditions	Patient Number	Study Type	Groups	Follow-up time	Results	Reference
			Control			
	58	Prospective	TPTD 20 μg daily × 3 months pre-op and 21 months post-op; BPs: alendronate 5 mg daily or risedronate 2.5 mg daily × 3 months pre-op and 21 months post-op	24 months	Bone fusion rate was significantly higher in the TPTD group (89%) than in the BPs group (77%)	Seki 2017 [25]
	62	Prospective	TPTD 20 μg daily × 2 months pre-op and 10 months post-op; BPs: risedronate 2.5 mg daily × 2 months pre-op and 10 months post-op	12 months	Incidence of pedicle screw loosening in the TPTD group (7%–13%) was significantly lower than that in the risedronate group (13%−26%) or control group (15%–25%) ($P < 0.05$). Incidence of pedicle screw loosening in the risedronate group was not significantly different from that in the control group ($P > 0.05$)	Ohtori 2013 [28]
	57	Prospective	TPTD 20 μg daily × 2 months pre-op and 8 months post-op; BPs: risedronate 17.5 mg daily × 2 months pre-op and 8 months post-op	12 months	Fusion rate was 82% in the TPTD group and 68% in the bisphosphonate group ($P < 0.05$). Time to fusion was 8 months in the TPTD group and 10 months in the bisphosphonate group ($P < 0.05$)	Ohtori 2012 [24]
Osteonecrosis of jaw (ONJ)	17	Case control	TPTD 20 μg daily × 1.8 months + BMP; BMP; Control	6 months	In all groups, the ONJ lesions were healed and new bone formation was detected in the cone beam CT images. The regeneration ratio was significantly greater in the group TPTD+BMP than in the BMP and control groups. Local application of BMP alone also had a beneficial effect on bone regeneration but was not more significant than control	Jung 2017 [34]
	24	Retrospective	TPTD 20 μg daily × 6 months; Control	6 months	The clinical improvement of ONJ was statistically better in the TPTD group after the 6-month treatment (60% in control group vs. 62.5% in TPTD group $p < 0.05$)	Kim 2014 [36]
	40	Prospective	TPTD 20 μg daily × 4 months	12 months		Bashutski 2010
Arthroplasty	40	Retrospective	TPTD 56.5 μg weekly × 12 months; Control: cementless total knee replacement	12 months	BMD (BMC/TV) was significant higher in TPTD group in the medial sites, but not lateral sites at 6, 9, and 12 months follow up	Kaneko 2016 [45]

Clinical Conditions	Patient Number	Study Type	Groups	Follow-up time	Results	Reference
	92	Retrospective	TPTD (non-specified dose) daily for 1 year; Control in cementless hemiarthroplasty in femoral neck fractures	3 months	The subsidence of the femoral stem tended to be significantly decreased in the TPTD group at 6 and 12 weeks post-operatively (p = 0.003 and p = 0.008, respectively)	Huang 2016 [46]
	48	Prospective	TPTD 20 μg × 12 months; Alendronate 35 mg weekly × 12 months; Control; cementless in total hip replacement	12 months	TPTD had an equal effect to alendronate in the prevention of periprosthetic BMD loss, but was superior to alendronate with regards to lumbar BMD improvement	Kobayashi 2016 [47]
	50	Prospective	TPTD 20 μg daily for 2 months post-op; Control in cemented total knee replacement	24 months	Median maximal total point motion from 12 to 24 months was similar in the 2 groups (TPTD: 0.14 mm vs. control: 0.13 mm)	Ledin 2017 [48]
Fracture healing	102	Case control	TPTD 40 μg daily × 2 months; TPTD 20 μg daily × 2 months; Control	42 weeks	Median time to fracture healing significantly shorter in the TPTD 20μg/day group (7.4 weeks), but not in the TPTD 40 μg/day group (8.8 weeks) compared with the placebo group (9.1 weeks) (p = 0.015)	Aspenberg 2010 [62]
	27	Case control	TPTD 40 μg daily × 2 months; TPTD 20 μg daily × 2 months; Control	5 weeks	Significant dose dependent improvement in radiographic callus assessment score (p < 0.001)	Aspenberg 2010 [63]
	65	Case control	TPTD 100 μg daily × 24 months; Control	24 months	Mean time to fracture healing significantly shorter in treatment group (7.8 weeks) versus control group (12.6 weeks; p < 0.001) Visual analog scale score for pain and the Timed ‘‘Up and Go’’ test improved in the treatment group versus the control group (p < 0.001)	Peichl 2011 [64]
Atypical femoral fracture (AFF)	15	Case series	TPTD 20 μg daily × 12 months	12 months	TPTD associated with improvement in bone turnover	Miller 2015 [75]
	6	Retrospective	TPTD 20 μg daily > 3 months + operation	24 months	Union completed radiologically median 5.4 months and clinically 5.7 months after the medication, respectively. Callus appeared abundantly showing median 1.4 of fracture healing response post-operatively	Kim 2016 [82]

Clinical Conditions	Patient Number	Study Type	Groups	Follow-up time	Results	Reference
	35	Retrospective	TPTD 20 μg daily or TPTD 56.5 μg (duration N/A)	>12 months	In subanalyses for all AFFs treated surgically, mean (± standard deviation) time to fracture healing significantly better in the TPTD group (5.4 ± 1.5 months) than in non- TPTD group (8.6 ± 4.7 months; P = 0.012), and frequency of delayed healing or non-union significantly lower in the TPTD group than in the non-TPTD group (P = 0.014)	Miyakoshi 2015 [71]
	14	Prospective	TPTD 20 μg daily × 24 months	24 months	No significant effect of TPTD on hip BMD, MS/BS or TBS and no consistent effect on fracture healing	Watts 2017 [68]
	14	Prospective	TPTD 20 μg daily × 6 months; Control	6 months	TPTD group was associated with 2-3-fold increase in bone remodeling markers (p = 0.01) and fracture healing. At the distal radius, the proportion of less densely mineralized bone increased by 29.5% (p = 0.01), and the proportion of older, more densely mineralized bone decreased by 16.2% (p = 0.03). Similar observations were made at the distal tibia	Chiang 2013 [72]
Non-union	3	Case Series	TPTD 20 μg daily × 3 months (2) & 9 months (1) following non-union diagnosis	3–9 months	All patients obtained union of femur fracture; no adverse events related to TPTD use were noted	Lee 2012 [69]
	1	Case Report	TPTD 20 μg daily × 8 months following non-union diagnosis	12 months	Radiographic evidence of complete union 4 months after treatment discontinuation	Xiaofeng 2017 [70]
	1	Case Report	TPTD 20 μg daily + revision surgery in setting of humeral non-union secondary to periprosthetic fracture	12 months	Radiographic evidence of complete fracture healing 1 year post-operatively	Emanuele 2017 [76]
	1	Case Report	TPTD 20 μg daily × 3 months + conservative treatment in setting of type III odontoid process fracture	6 months	3 mo CT revealed partial fracture healing and near complete recalcification of fracture gap 6 mo CT revealed complete fracture healing	Bednar 2013 [77]
Stress fracture	2	Case Series	TPTD (non-specified dose) daily × 1 month in setting of metatarsal stress fracture	1 month	1 mo radiographs revealed bony callus and new bone formation in both patients	Raghavan 2012 [79]
	1	Case Report	TPTD 20 μg daily × months 1–5 and 7–16 following stress fractures in setting of hypophosphatasia	24 months	Radiographic evidence of fracture repair 2–4 months after treatment onset. Hypophosphatasemia and hypophosphatemia corrected	Whyte 2007 [80]

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; BPs: bisphosphonates; BS, bone surface; MS, mineral surface; TBS, trabecular bone score; TPTD, teriparatide; TV, total volume; AFFs: Atypical femoral fractures; BMP: bone morphogenetic protein; CT: computed tomography; ONJ: osteonecrosis of jaw