Review Article

Applications of Teriparatide for Alveolar Bone Regeneration: A Systematic Review

Rupali Agnihotri[1], Sumit Gaur[2]

[1]Departments of Periodontology, [2]Pedodontics and Preventive Dentistry, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka 576104, India

Received : 23-05-21
Revised : 10-08-21
Accepted : 18-08-21
Published : 30-11-21

ABSTRACT

Aim: The aim of this study was to systematically review the applications of teriparatide (TP) for alveolar bone regeneration in oral cavity. **Materials and Methods:** An electronic search of the data was conducted in Medline (PubMed), Scopus, Web of Science, and Embase. The original research associated with the applications of TP for alveolar bone regeneration was evaluated. Cochrane's tool [for human randomized controlled trials (RCTs)] and SYRCLE's tool (for animal RCTs) were used to assess the risk of bias. About two human and four animal studies had low risk of bias. **Results:** The results from the 11 studies that were included in the review showed that TP enhanced alveolar bone formation in osteonecrosis of jaws, chronic periodontitis (CP), osseointegration of dental implants as well as orthodontic tooth movement. **Conclusion:** The TP may be applied for alveolar bone regeneration in osteonecrosis of jaws and CP. However, further human clinical trials are required to verify its applications and adverse effects in various oral bone conditions.

Keywords: *Alveolar bone, osseointegration, osteonecrosis, regeneration, teriparatide*

Introduction

Bone loss in oral cavity may occur due to local or systemic reasons. Among them, chronic periodontitis (CP) is the leading cause for alveolar bone resorption and soft tissue attachment loss while some residual ridge resorption also occurs following tooth extraction.[1,2] Systemic conditions such as osteoporosis and rheumatoid arthritis affect alveolar bone density and tooth support in jaws.[3]

The bone-sparing agents such as bisphosphonates have been traditionally applied in subjects with osteoporosis to increase bone mineral density (BMD).[4] However, they induce complications such as osteonecrosis of jaws in case of exposure to oral surgical procedures such as tooth extractions or periodontal surgery.[5] Recently, agents that stimulate neo bone formation like teriparatide (TP), a biosynthetic human parathyroid hormone (PTH) consisting of its first 34 amino acids, have been applied in this direction.[4,6] It is a systemic osteoanabolic agent also investigated for oral bone regeneration.[1,4] It increases BMD and reduces the risk for fractures as it stimulates new bone formation. This is mainly related to its effects on osteoblasts, increased renal tubular re-absorption of calcium and excretion of phosphate, and an indirect increase in intestinal absorption of calcium via an effect on 1,25-dihydroxyvitamin D.[4] Besides, immunolabeling analysis has shown that TP increases the expression of Wnt (wingless-type MMTV integration site family), alkaline phosphatase (ALP), and osteocalcin with reduction of tartarate-resistant acid phosphatase (TRAP) activity.[3] The Wnt signaling is essential for osteoblast proliferation and differentiation, which further supports bone formation.[3]

Owing to these bone anabolic effects, TP is widely being explored for alveolar bone regeneration. With

Access this article online

Quick Response Code:

Website: www.jispcd.org

DOI: 10.4103/jispcd.JISPCD_169_21

Address for correspondence: Dr. Sumit Gaur, Department of Pedodontics and Preventive Dentistry, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka 576104, India.
E-mail: get2sumitgaur@yahoo.co.in; sumit.gaur@manipal.edu

How to cite this article: Agnihotri R, Gaur S. Applications of teriparatide for alveolar bone regeneration: A systematic review. J Int Soc Prevent Communit Dent 2021;11:639-43.

this background, the present systematic review aims to evaluate the applications of TP for alveolar bone regeneration in oral cavity.

Materials and Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to identify the research publications related to the role of TP for alveolar bone regeneration in oral cavity. The databases searched were Medline (PubMed), Scopus, Embase, and Web of Science till March 17, 2021. A combination of keywords such as "Teriparatide" AND "Alveolar bone" AND "Bone" OR "Periodontitis" OR "Osteonecrosis" AND "Jaws" were used. They were verified in the titles, abstracts, or keywords during the initial search. It resulted in a total of 64 articles (63 through electronic search and 1 article through manual search)[7] [Figure 1]. The data were screened for duplicates which resulted in 35 articles wherein the titles and abstracts were read.

Inclusion and exclusion criteria

The eligibility criteria included free full text of original studies in English related to the role of TP for alveolar bone regeneration. Any kind of recommendations, *in vitro* studies, expert statements, reviews, technical reports, case reports, and non-original papers were excluded. This resulted in four human and seven animal studies that were included in the review.[1,3-12]

Data extraction

The type of study, their aims and objectives, salient features, results, and conclusions were recorded.

Risk of bias assessment

Two independent review authors (RA and SG) assessed the risk of bias in human studies with the help of Cochrane's tool for randomized controlled clinical trials (RCTs).[13] The non-randomized interventional study was assessed with the help of the National Institutes of Health quality assessment tool for before-after (pre-post) study with no control group.[14] The RCTs involving animals were evaluated using SYRCLE's tool.[15] The disagreements were resolved by discussion.

Results

About four human and seven animal studies were included in the review[1,3-12] [Table 1]. Two human RCTs had a low risk of bias,[1,6] whereas one RCT and one non-randomized interventional study had unclear risk of bias.[4,7] There were five animal RCTs, of which four had low risk of bias[5,9-11] and the remaining had unclear risk of bias[3,8,12] [Figure 2]. The results thus obtained are summarized as follows.

A. Type of studies

Three human and five animal studies were RCTs,[1,5-11] whereas one human study was non-RCT.[4]

B. Type of oral conditions treated with TP

In humans, TP was evaluated for its effects on alveolar bone regeneration in medication-related osteonecrosis of jaw (MRONJ), severe CP, and osseointegration around the dental implants.[1,4,6,7] In preclinical studies, orchiectomy or ovariectomy of rats was done to evaluate the effects of TP on alveolar bone healing in experimental osteoporotic or MRONJ animals, when subjected to oral surgical procedures.[3,8,10] Besides, its effects on alveolar bone remodeling were evaluated in

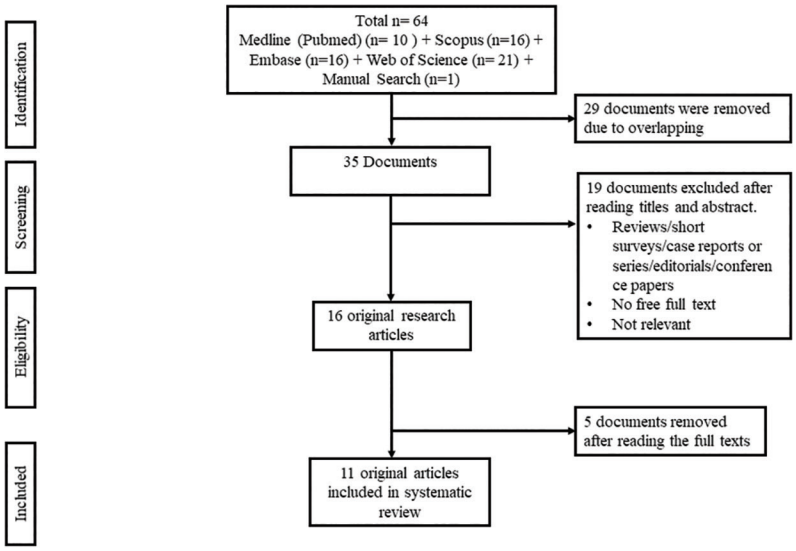

Figure 1: Evidence search on the applications of TP in regeneration of alveolar bone as per the PRISMA guidelines

induced osteoporotic animals undergoing orthodontic tooth movement.[12]

C. Dosage of TP and duration of therapy

In humans, TP was administered as 20 µg daily subcutaneous injection in all the studies.[1,4,6,7] The average duration of treatment ranged from 28 days to 8 weeks. In severe CP, the therapy was started 3 days before the surgery and continued for 6 weeks.[1] It was prescribed for an average of 2–12.4 months in osteonecrosis of jaws.[4,6] For osseointegration, self-administered injections were prescribed for 28 days after implant placement.[7]

In animal models, the dose of TP was higher than the clinical dosage in humans. The doses were 2,[10] 3,[11] 10,[10,11] 20,[9,10] and 30 µg/kg/day.[3,5,8,11,12] It was suggested that 4 weeks of TP therapy, beginning at the same day or 2 weeks before tooth extraction, could prevent osteonecrosis of jaws.[9]

D. Bone biomarkers and histochemistry analysis

In humans, the levels of bone-specific alkaline phosphatase (BAP), 25-hydroxyvitamin D, and calcium were evaluated along with bone formation biomarkers such as procollagen type-1 N-propeptide (P1NP), osteocalcin, and pyridinoline cross-linked carboxy-terminal propeptide of type-1 procollagen (ICTP).[1,4,6] Besides, bone resorption biomarker C-terminal telopeptide of type-1 collagen (CTX) was evaluated.[4,6] In severe CP and MRONJ, TP increased BAP, 25-hydroxyvitamin D, and P1NP transiently at 6 weeks.[1] The CTX levels were reduced.[4,6]

In animal models, TP increased relative gene expression of receptor activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) initially.[8,11] However, at 42 days, the RANKL levels decreased with increased OPG and reduced RANKL to OPG ratio.[8] Further, bone resorption markers such as Dickkopf-related protein 1 (DKK1) and sclerostin were reduced and β catenin increased.[11] Elevated Wnt protein levels were evident in tooth socket of osteonecrosis groups treated with the TP.[3] Their levels of ALP and osteocalcin were also increased.[3] In TP groups, more number of TRAP-positive osteoclasts was observed in apoptotic phase.[5,11]

Table 1: Studies reporting various applications of TP in alveolar bone regeneration

Condition requiring alveolar bone regeneration	Human study	Animal study
Osteonecrosis of jaws (medication/bisphosphonate-related)	Kakehashi *et al.*,[4] Sim *et al.*[6]	Ersan *et al.*,[5] Zandi *et al.*,[9,10] Yu and Su[11]
Chronic periodontitis	Bashutski *et al.*[1]	
Osseointegration of dental implants	Kuchler *et al.*[7]	
Orthodontic tooth movement		Salazar *et al.*[12]
Osteoporosis		de Oliveira Puttini *et al.*,[8] de Oliveira *et al.*[3]

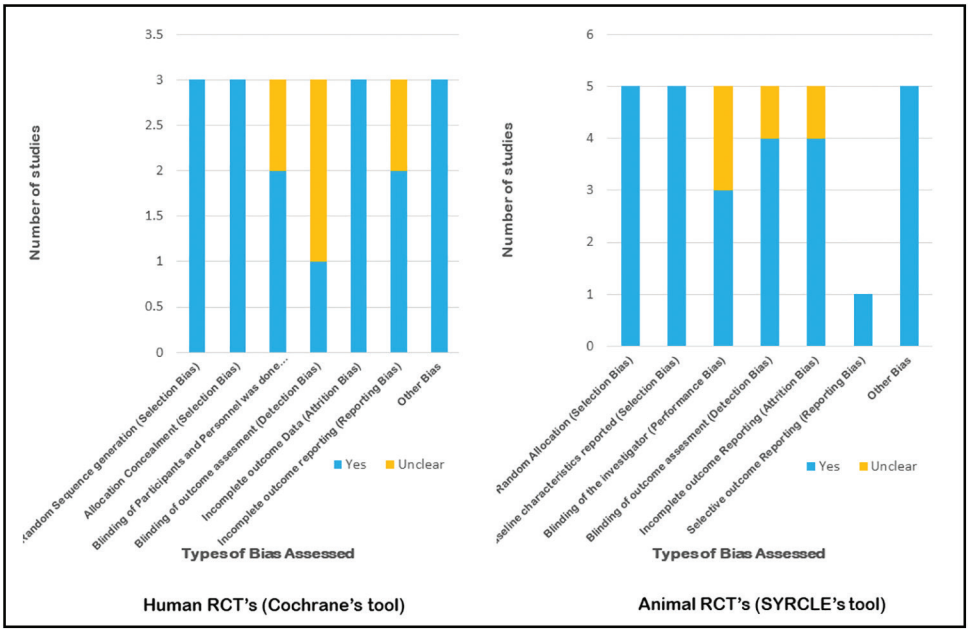

Figure 2: Risk of bias summary in human and animal RCTs

E. BMD analysis

In human studies, the systemic effects of TP on BMD were estimated from dual-energy X-ray absorptiometry (DXA) scans of spine and femur.[1,4] A radiographic evidence of greater bone gain and new bone formation was observed in both CP and MRONJ.[1,4,6] The cone beam computed tomography imaging also revealed increased bone volume.[6] Besides, in 18F-fluoride Positron Emission Tomography and CT (PET-CT), there was greater uptake of fluoride in TP groups, suggesting increased bone formation.[6]

Similarly, in animal studies, micro-CT analysis of osteonecrotic jaws treated with TP had greater bone volume, mineral deposition rate, and reduced porosity.[3,5,8,11] In bisphosphonates-induced osteonecrosis of jaws, 10 µg/kg/day of TP resulted in highest bone volume.[11]

F. Histological and histomorphometric examination

In humans, histomorphometric analysis of study implants retrieved from 23 participants after 9 weeks showed that TP promoted greater new bone formation from the pre-existing bone.[7]

In animal models, TP resulted in bone formation with smaller areas of connective tissue and greater soft tissue healing in osteopenic rats.[8-10] Furthermore, its moderate-to-high dosage for 4 and 8 weeks reduced the number of empty lacunae and increased osteocyte numbers.[9-11] However, very high dosage resulted in greater proportion of empty lacunae.[11] TP also supported orthodontic tooth movement in ovariectomized rats.[12]

G. Changes in clinical and other parameters

In human studies, TP improved periodontal parameters such as probing depth, clinical attachment level, and bleeding on probing in severe CP.[1] It also enhanced osseointegration around the titanium implants.[7] Further, it reduced clinical signs and symptoms of MRONJ.[4] The oral health-related quality of life scores (validated through Oral Health Impact Profile questionnaire) were improved in MRONJ subjects on TP therapy.[1,6]

H. Adverse events

In human studies, mild gastrointestinal symptoms, musculoskeletal pain, and injection site reactions were reported.[1,4,6] Further, no new malignancies or worsening of pre-existing malignancies were reported with TP.[6]

Discussion

The results from the studies included in the review suggest that TP is a promising systemic bone anabolic agent. It supports alveolar bone regeneration in MRONJ, severe CP, dental implants, and orthodontic tooth movement.[1,4,6,7,12]

MRONJ usually develops following invasive dental procedures in osteoporotic individuals on bisphosphonates, which are structurally similar to pyrophosphates and bind to hydroxyapatite in bone.[4,16] Following surgical procedures, they are taken up by osteoclasts which then undergo apoptosis. Subsequently, the osteoclasts are unable to remove dead bone resulting in osteonecrosis.[5] The TP enhances bone remodeling in wound healing areas and activates living bone turnover which hastens sequestrum separation. Therefore, it may be indicated in osteoporotic patients when they require surgical dental treatments.[8] These beneficial effects of TP were observed in animal studies also.[11]

TP promotes orthodontic tooth movement in osteoporotic rats by increasing cortical bone area and density. It may be used as an alternative to bisphosphonates in osteoporotic subjects undergoing orthodontic treatment.[12] Similar outcomes were observed with intermittent PTH therapy during orthodontic tooth movement in rats with periodontitis.[17]

In animal studies, significantly higher doses of TP were applied due to differences in hormone metabolism between humans and rats.[10] The intermittent low dosages of TP enhanced bone formation which was dependent on frequency of its administration.[10,11] This dosing regimen created an "anabolic window," whereby bone formation is stimulated before a secondary increase in bone resorption.[5,11] This effect is specifically useful for early osseointegration of dental implants and in severe CP.[1,7] Therefore, adjunctive daily 20 µg subcutaneous injection of TP for 4–8 weeks may accelerate osseous wound healing due to its osteoanabolic effect in the craniofacial region in MRONJ.[1,6,7] As TP preferentially enhances bone turnover at surgical sites, it may be effective for oral surgical procedures.[1] For instance, a 6-week regimen of TP promoted bone formation at wound site for up to 12 months due to increased activity and number of osteoblasts.[1]

The osteoanabolic effect of TP is evident as various bone formation biomarkers (e.g., BAP, P1NP, ALP, and osteocalcin) increased after therapy.[1,4,6] For instance, TP administration increased the levels of RANKL and OPG at 42 days after extraction.[8] Similarly, the Wnt expression which signals osteogenesis was increased with reduced expression of bone sclerostin and DKK1.[3,11] Furthermore, the microstructural characteristics of alveolar bone such as enhanced bone volume, trabecular thickness, separation, number, and porosity were improved.[3] Improved periodontal healing has also been observed with the combination therapy of intermittent systemic PTH and neutral self-assembling peptide hydrogel in animals.[18]

Although TP is a promising bone anabolic agent, it is contraindicated in bone metastasis, osteosarcoma, high nitrogen containing bisphosphonates, or corticosteroids.[4] Although animal studies have reported development of osteosarcoma with TP, it was not established in humans.[4,6] Furthermore, it is an expensive drug that requires prolonged administration for not more than 2 years in cases of MRONJ.[4]

Even though adjunctive therapy with TP promotes alveolar bone regeneration in both CP and osteonecrosis of jaws, these results should be applied cautiously as only animal studies and three human RCTs were included in this review. Further, human RCTs evaluating its clinical applications are required to verify these results.

Conclusion

Even though teriparatide is a promising bone anabolic agent for alveolar bone regeneration, there are potential challenges to its applications. Prospective clinical trials in humans that target different oral bone conditions are warranted. Furthermore, verification of its potential adverse effects should be done through studies involving larger populations with oral osseous defects. Future, local drug delivery systems may be developed which would help in concentrating the drug within the localized bone defect and enhance bone formation.

Acknowledgements

Not applicable.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Author's contribution

Both the authors equally contributed to the paper.

Ethical policy and institutional review board statement

Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

Not applicable.

References

1. Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, Braun TM, *et al*. Teriparatide and osseous regeneration in the oral cavity. N Engl J Med 2010;363:2396-405.
2. Hansson S, Halldin A. Alveolar ridge resorption after tooth extraction: A consequence of a fundamental principle of bone physiology. J Dent Biomech 2012;3:1758736012456543.
3. de Oliveira D, de Oliveira Puttini I, Silva Gomes-Ferreira PH, Palin LP, Matsumoto MA, Okamoto R. Effect of intermittent teriparatide (PTH 1-34) on the alveolar healing process in orchiectomized rats. Clin Oral Investig 2019;23:2313-22.
4. Kakehashi H, Ando T, Minamizato T, Nakatani Y, Kawasaki T, Ikeda H, *et al*. Administration of teriparatide improves the symptoms of advanced bisphosphonate-related osteonecrosis of the jaw: Preliminary findings. Int J Oral Maxillofac Surg 2015;44:1558-64.
5. Ersan N, van Ruijven LJ, Bronckers AL, Olgaç V, Ilgüy D, Everts V. Teriparatide and the treatment of bisphosphonate-related osteonecrosis of the jaw: A rat model. Dentomaxillofac Radiol 2014;43:20130144.
6. Sim IW, Borromeo GL, Tsao C, Hardiman R, Hofman MS, Papatziamos Hjelle C, *et al*. Teriparatide promotes bone healing in medication-related osteonecrosis of the jaw: A placebo-controlled, randomized trial. J Clin Oncol 2020;38:2971-80.
7. Kuchler U, Luvizuto ER, Tangl S, Watzek G, Gruber R. Short-term teriparatide delivery and osseointegration: A clinical feasibility study. J Dent Res 2011;90:1001-6.
8. de Oliveira Puttini I, Gomes-Ferreira PHDS, de Oliveira D, Hassumi JS, Gonçalves PZ, Okamoto R. Teriparatide improves alveolar bone modelling after tooth extraction in orchiectomized rats. Arch Oral Biol 2019;102:147-54.
9. Zandi M, Dehghan A, Mohammadi-Mofrad A, Amini P, Vahdatinia F. Short-term perioperative teriparatide therapy for the prevention of medication-related osteonecrosis of the jaw: A randomized, controlled preclinical study in rats. J Craniomaxillofac Surg 2017;45:275-80.
10. Zandi M, Dehghan A, Zandipoor N, Amini P, Doulati S. Effect of different doses and durations of teriparatide therapy on resolution of medication-related osteonecrosis of the jaw: A randomized, controlled preclinical study in rats. J Craniomaxillofac Surg 2018;46:466-72.
11. Yu W, Su J. The effects of different doses of teriparatide on bisphosphonate-related osteonecrosis of the jaw in mice. Oral Dis 2020;26:609-20.
12. Salazar M, Hernandes L, Ramos AL, Micheletti KR, Albino CC, Nakamura Cuman RK. Effect of teriparatide on induced tooth displacement in ovariectomized rats: A histomorphometric analysis. Am J Orthod Dentofacial Orthop 2011;139:e337-44.
13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al*. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training [Internet]. Cochrane Handb Syst Rev Interv version 6.0, 2019 [cited February 1, 2021]. Available from: https://training. cochrane.org/handbook/current. [Last accessed on 1 Feb 2021].
14. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? Mil Med Res 2020;7:7.
15. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43.
16. Chiu WY, Yang WS, Chien JY, Lee JJ, Tsai KS. The influence of alendronate and tooth extraction on the incidence of osteonecrosis of the jaw among osteoporotic subjects. PLoS ONE 2018;13:e0196419.
17. Zhang C, Li T, Zhou C, Huang L, Li Y, Wang H, *et al*. Parathyroid hormone increases alveolar bone homoeostasis during orthodontic tooth movement in rats with periodontitis via crosstalk between STAT3 and β-catenin. Int J Oral Sci 2020;12:38.
18. Yoshida W, Matsugami D, Murakami T, Bizenjima T, Imamura K, Seshima F, *et al*. Combined effects of systemic parathyroid hormone (1-34) and locally delivered neutral self-assembling peptide hydrogel in the treatment of periodontal defects: An experimental *in vivo* investigation. J Clin Periodontol 2019;46:1030-40.