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Management of bisphosphonate-related osteonecrosis of the jaw using teriparatide treatment: A systematic review

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SUMMARY

Objective. To systematically review the current literature and determine whether the additional TPTD administration for patients with BRONJ is an effective treatment modality.

Material and methods. The systematic review was registered in the PROSPERO (CRD42021242796) and conducted according to the PRISMA statement. An electronic search was performed using MEDLINE (PubMed), ScienceDirect, The Cochrane Library and LILACS databases using a combination of the keywords "Bisphosphonate-Associated Osteonecrosis of the Jaw"[Mesh], "treatment" to identify studies published from 2010.

Results. The authors found 8 articles that met the inclusion criteria of this systematic review. According to two studies, TPTD was statistically significantly associated with a greater BRONJ lesion resolution, compared to control group ($p<0.05$). However, one article showed no significant difference in proportion of resolved lesions ($p=0.478$). Regarding the effectiveness of TPTD treatment according to administration frequency, daily injection group showed no significant changes in the clinical stage of BRONJ, no difference in the percentage of bone formation on patients osteolysis, compared to weekly injections. Concerning bone resorption/regeneration markers, all the included studies showed that bone resorption markers significantly increased after 3-month TPTD administration. In a study which used multivariate analysis between TPTD and non-TPTD groups using age, BMI, duration of BP usage, the difference in s-OC values after 3 months of the treatment was significant ($p<0.05$).

Conclusion. This review provides evidence for the potential benefits of additional TPTD administration for patients with BRONJ being an effective treatment modality.

Keywords: teriparatide, diphosphonates, bisphosphonate-associated osteonecrosis of the jaw, osteonecrosis.

INTRODUCTION

Over the years, BPs have proven to be clinically beneficial for their effect in conditions where an imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption underlies disease pathology. Hence, bisphosphonates (BPs) are acknowledged to be the most prescribed drug for osteoporosis treatment worldwide (1). This medication is also effective for skeletal and oncological diseases such as lung, prostate, and breast cancers, hypercalcemia, multiple myeloma, and Paget's disease (2). In the USA alone 22 million prescriptions of alendronate (intraoral BP) were issued from 2003 to 2004 (1). Meanwhile, in 2006, 190 million intraoral BP units were prescribed worldwide (3). In comparison to 14.7 million intraoral (BP) medications ordered for patients in 2012 in the USA (4).

BPs are reliable medication for treatment of oncological and metabolic pathologies. Nevertheless, the bisphosphonate-related osteonecrosis of the jaw (BRONJ) may occur as a complication (5). BRONJ is defined as a diffuse bone disease characterized by the presence of bone exposed to the oral cavity that does not heal within 8 weeks of observation and conventional treatment, in patients under or who have taken BP therapy, with no history of radiation therapy in the head and neck region (6). The etiology and pathogenesis of BRONJ is associated with

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numerous factors including constant mechanical trauma, local infection, periodontal surgery, and tooth extractions (7, 8). Nevertheless, the management of BRONJ remains a controversial topic in the oral surgery field, as the current consensus on treating BRONJ patients is based on the conservative approach, mainly focusing on symptomatic treatment. To understand it better, the staging and treatment of BRONJ are brought out in (Table 1), provided in the systematic review by Gelazius *et al* (9).

Teriparatide (TPTD) is a synthetic version of the human parathyroid hormone, composed of its 1-34 N-terminal fragment. It is currently the only anabolic agent approved by the FDA, that directly stimulates bone formation by having an ability to activate pre-existing osteoblasts, increased differentiation of lining cells, and reduced osteoblast apoptosis, followed by activation of osteoblast. This leads to an increased bone mineral density. In several animal studies, the results have shown the potential of TPTD to increase bone mass, bone diameter, bone strength, and structural integrity. The efficacy of TPTD therapy has been assessed in human studies, involving postmenopausal women (10). Findings have reported that TPTD is a clinically viable approach for enhancing bone regeneration against bone defects and fractures. To this day, several studies have investigated the efficacy of TPTD administration to treat BRONJ and disclosed favourable outcomes. However, no systematic reviews have been carried out regarding this topic. Therefore, the aim of this article is to systematically review the current literature on influence of TPTD administration in treatment of BRONJ patients.

MATERIAL AND METHODS

Protocol and registration

A systematic review was based on the PRISMA guidelines (11). The protocol for the systematic review was registered in the PROSPERO (International prospective register of systematic reviews) database. Registration number: CRD42021242796.

Focused question

The following focused question was developed with reference to the PICOS model: Does administration of teriparatide treatment as an adjunct improve mandibular and maxillary jaw regeneration in patients diagnosed with BRONJ?

- Population (P) – patients diagnosed with BRONJ.
- Intervention/Exposure to a risk factor (I) – administration of teriparatide treatment as an adjunct.
- Control (C) – conservative or surgical BRONJ treatment.
- Outcome (O) – improvement of mandibular and maxillary jaw regeneration.

Search strategy

On 30 November 2020, a systematic search in the medical literature was carried out to identify all peer-reviewed articles, reported from 2010 to 2020. Combinations of keywords "Bisphosphonate-Associated Osteonecrosis of the Jaw"[Mesh], “treatment” were used in the following electronic bibliographic databases: MEDLINE (searched via PubMed), EMBASE (searched via ScienceDirect), System for Information on Grey Literature in Europe, The Cochrane Library (Cochrane Central Register of Controlled Trials) and LILACS. Additionally, the search was expanded by checking for potential articles in the references of the included articles. No language restrictions were applied if an English summary was provided.

Study selection and data collection process

Two independent authors conducted an electronic search and after revision of titles and abstracts selected studies that met the inclusion criteria. The final selection was made after assessing full-text studies. In case of differing opinions during the study screening process third reviewer made final decision.

Inclusion criteria

- Retrospective studies, cohort studies, case-control studies, cross-sectional studies;
- Patients that are diagnosed with BRONJ;
- Patients that used teriparatide treatment as an adjunct to conservative or surgical treatment;
- Follow-up of at least 3 months;
- Articles were published less than 10 years ago.

Exclusion criteria

- Systematic reviews, meta-analyses, case series, case reports, letters to the editor, in vitro studies, animal studies, experimental studies, reviews, conference abstracts, guidelines;
- Prior treatment with radiotherapy of head/neck region;
- Patients treated with glucocorticosteroids;
- Studies of adolescents (under 18 years of age) and elderly people (older than 80);
- Articles older than 10 years old.

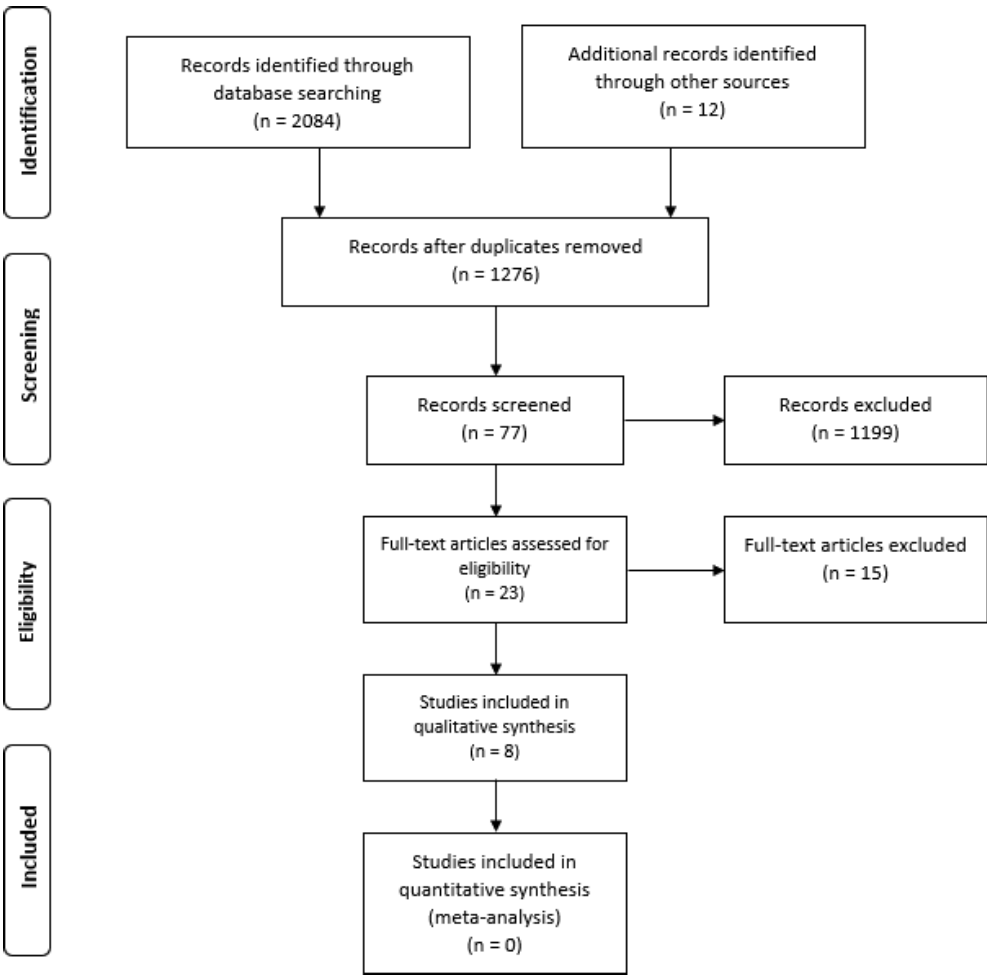

Fig 1. Prisma flow chart

Methodological quality

For evaluation of the risk of bias level and overall quality in RCT studies, RoB 2 tool was used (12). This Cochrane risk-of-bias tool is for randomized trials and assesses the following aspects: randomization process, deviations from intervention, missing outcome data and its measurement, and selection of the reported results.

The ROBINS-I tool of the Cochrane Collaboration (13) was used to assess the general quality and the risk of bias in retrospective studies, evaluating confounding, selection of the participants in the study, classifications of interventions, deviation from intended interventions, missing data, measurement of the outcome, and selection of the reported result.

For case reports, an Appraisal checklist was used to assess the risk of bias and general quality (14).

Synthesis of the results

A narrative summary of included studies was made. The generated data presented their study design, number of patients, treatment methods, follow-up duration, and treatment outcomes.

RESULTS

Study selection

The procedure of study selection was depicted using the Prisma Flow chart in (Figure 1). 2096 articles were shown after the initial electronic databases search. After removal of duplicates

Table 1. Staging and treatment of BRONJ according to reviewed studies*

Risk category	No clinical/radiological evidence of exposed bone or infection/inflammation.
Treatment plan	No surgical treatment is needed. Patient has to be informed about following risks. Good oral hygiene with re-examinations at least once every 6 months should be done.
Stage I	Clinical evidence of exposed bone for more than 8 weeks. This stage is usually asymptomatic. No signs infection is normally seen.
Treatment plan	No surgical treatment is needed. Antibacterial mouth rinses, professional oral hygiene with no injury of exposed bone can be considered, common follow ups for exposed bone re-evaluation. Antibiotic treatment can be prescribed if patient's condition is difficult.
Stage II	Exposed/ necrotic bone with signs of infection, drainage of inflammatory matter can appear.
Treatment plan	Management of pain, broad-spectrum antibiotics, antibacterial mouthrinses. Debridement of necrotic bone surface area, common follow ups with professional oral hygiene and re-evaluation of necrotic bone. Drug holidays may be considered as an option.
Stage III	Exposed' necrotic bone with sings of infection. Extraoral fistula, pathological fractures can appear.
Treatment plan	Antibacterial mouthrinses and broad spectrum antibiotics with pain management to prepare patient for surgical intervention-resection of necrotic bone. Drug holidays may be considered as an option.

*Stages applies for patients, who used or are using intraoral/intravenous bisphosphonates. And had no history of radiotherapy of head/neck.

the titles of 1276 studies were screened for eligibility, 77 articles were chosen in this stage. 54 articles were excluded having read their abstract. After applying all the filters and reading full-text articles, 8 articles fit our inclusion criteria and were included in this systematic review. The final sample consisted of 3 randomized controlled trials (15-17), 3 retrospective studies (18-20), and 2 case series (21, 22).

Study characteristics

Characteristics of all 8 publications included in the review are presented in (Table 2). The articles were published between the years 2011 and 2020. The number of patients varied from 6 to 34 (a total of 139 patients in 8 studies) with patients' mean age being 75, 47 years. Follow-up duration in the included studies ranged from 3 up to 26 months. 62.8% patients used alendronate, 21.3% patients used risedronate, 6.4% – minodronate, 4.3% – ibandronate, 2.1% – zoledronate, 2.1% – denosumab, 1% – pamidronate.

Quality analysis

For RCTs risk of bias level assessment and the overall quality was performed using Cochrane Collaboration's RoB 2 tool (12). Two RCTs had a low risk of random sequence generation while 1 study had a high risk (15). In the allocation concealment and blinding section, one study had a low risk of bias (17), while two had a high risk (15, 16). In attrition bias (incomplete outcome data), the bias of outcome data measurement, and reporting bias (selective reporting) all 3 studies had a low

Table 2. Data selection

Author, year	Study design	No. of patients	Treatment methods	Follow-up duration	Outcome
Sim *et al*., 2020 (17)	RCT	34	G1: TPTD injections for 8 weeks; G2: placebo injections.	12 months	Teriparatide was associated with a greater rate of resolution of BRONJ lesions; Teriparatide was also associated with reduced bony defects at week 52
Ohbayashi *et al*., 2019 (16)	RCT	12	G1: weekly TPTD injections for 6 months; G1: daily TPTD injections for 6 mos.	6 months	TPTD treatment with BRONJ led to partial remission or complete remission in 5 daily-group patients and 3 weekly group patients. The weekly group did not show significant improvement, but the daily group did.
Jung *et al*., 2017 (15)	RCT	17	G1: TPTD+BMP; G2: BMP; G3: control	3 months	Significantly greater amount of bone formation in CBCT imaged was observed in the group PTH+BMP than in the BMP and control groups.
Kim *et al*., 2014 (18)	Retrospective	24	G1: daily TPTD injections for 6 months; G2: control	6 months	The clinical improvement of BRONJ was statistically better in the TPTD group after the 6-month treatment ($p<0.05$). Moreover, patients with higher baseline serum 25 (OH)D levels showed better clinical therapeutic outcomes with TPTD.
Morishita *et al*., 2020 (19)	Retrospective	29	Daily TPTD injections	up to 26 months	Treatment outcomes were evaluated as effective in 75.9% of patients with complete resolution in 65.5%.
Pelaz *et al*., 2014 (20)	Retrospective	9	G1: PRF; G2: TPTD daily injections.	6 months	The PRF showed better results than teriparatide in the treatment of recurrent BRONJ.
Kwon *et al*, 2012 (21)	Case series	6	Daily TPTD injections	3 months	s-OC values were significantly elevated within 2 months after teriparatide treatment and the BRONJ lesions were healed. S-CTX values were also elevated in four patients, whereas those of the rest two patients stayed within minimal change. The change was marginally significant at 3 months
Kakehashi *et al*., 2015 (22)	Case series	8	Daily TPTD injections	over 6 months	Of the eight cases, seven exhibited clinical improvement of the jaw-related symptoms of osteonecrosis and progression of the sequestration, while one case did not show improvement of the symptoms. Administration of teriparatide in patients with osteonecrosis of the jaw promotes bone formation and subsequent sequestration over a short period of time.

risk (15-17). Detailed information is presented in (Table 3).

The risk of bias for retrospective studies was performed with the ROBINS-I tool (13). It showed that one study had a low risk of bias, and two studies had a high risk of bias in confounding and selection of the participants in the study. Considering the classification of the interventions, a study by Kim *et al*. (18) had a high risk of bias, while a study by Pelaz *et al*. (20) had a high risk of bias in deviations from intended interventions. All of the studies had a low risk of bias in missing data, measurement of the outcome, and selection of the reported result (18-20). Detailed information is presented in (Table 4).

All of the included case reports showed high appraisal (21, 22). Detailed information is presented in (Table 5).

A qualitative synthesis of the results

Resolution of BRONJ lesions

According to a study by Sim *et al*. (17), TPTD was significantly associated with a greater rate of BRONJ lesion resolution, compared to placebo treatment (p=0.013). However, the study results showed no significant difference in the proportion of resolved lesions (p=0.478) (17). In the study by Kim *et al*. (18), it was noted that the improvement in BRONJ status was significantly better in the TPTD group (p<0.05). Results showed that 62.5% of the patients in the TPTD group showed moderate improvement and 37.5% marked improvement, while in the non-TPTD group 40% demonstrated moderate improvement, and 0% marked improvement (18). In the case report that consisted of 6 patients, the administration of TPTD resulted in a complete

Table 3. Randomised clinical trials' risk of bias level assessment using Cochrane Collaboration's RoB 2 tool

Study	Year of publication	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Sim *et al*. (17)	2020	Low	Low	Low	Not clear	Low	Low	Low
Ohbayashi *et al*. (16)	2019	Low	High	High	Low	Low	Low	Low
Jung *et al*. (15)	2017	High	High	High	Low	Low	Low	Low

Table 4. Retrospective studies' risk of bias level assessment using ROBINS-I tool

Study	Year of publication	Confounding	Selection of the participants in the study	Classification of the interventions	Deviations from intended interventions	Missing data	Measurement of the outcome	Selection of the reported result
Kim *et al*. (18)	2014	Low	Low	High	Low	Low	Low	Low
Morishita *et al*. (19)	2020	High	High	Low	Low	Low	Low	Low
Pelaz *et al*. (20)	2014	High	High	Low	High	Low	Low	Low

Table 5. Case reports' risk of bias level assessment using an Appraisal checklist

Appraisal checklist	Study	
	Kwon et al., 2012 [21]	Kakehashi et al., 2015 [22]
Were the patient's demographic characteristics clearly described?	Yes	Yes
Was the patient's history clearly described and presented as a timeline?	Yes	Yes
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
Was the intervention (s) or treatment procedure (s) clearly described?	Yes	Yes
Was the post-intervention clinical condition clearly described?	Yes	Yes
Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes
Does the case report provide takeaway lessons?	Yes	Yes
Overall appraisal: [Yes/No/Unclear/Not applicable]	Yes	Yes

recovery of BRONJ lesions, with coverage of the exposed bone by mucosa (21).

Bone resorption/regeneration markers

In the study by Sim *et al*. (17), TPTD treatment was associated with an increased bone volume and a reduced defect size in a greater proportion of patients after 52 weeks (80% TPTD vs 31.3% placebo, p=0.017). TPTD was also associated with a 3-fold Procollagen 1 Intact N-Terminal Propeptide (P1NP) increase compared to placebo after 4 and 8 weeks (p=0.01). Also, those who were randomly assigned to TPTD therapy seemed to have increased uptake on 18F-fluoride PET-CT scans, as measured by both standardized uptake value and kinetic models and defined as a 25% increase in uptake.

Four of the included studies evaluated s-CTX levels in patients afterwards treatment with TPTD (15, 17, 18, 21). In a study by Sim *et al*., results showed that TPTD was associated with a 30% increase in CTX after 8 weeks period (17). In the publication by Jung *et al*., the values of s-CTX increased at 1st and 3rd months of the treatment with TPTD by 3 times, and the values were statistically different from the control group ($p<0.05$) (15). Likewise, the results by Kim *et al*. showed that Serum CTX values exhibit a later but much larger increasing pattern, while no significant changes occurred in the non-TPTD group (18). Compared to the non-TPTD group, TPTD treatment significantly increased s-CTX levels ($p<0.05$ for 3 and 6 months). In the case report by Kwon *et al*., which includes 6 cases, S-CTX values also increased in four patients, whereas the rest of the two patients showed minimal change in their s-CTX values and the change was not statistically significant, but the change was marginally significant between the mean values at baseline and 3 months (p=0.018) (21).

Three of the included studies measured s-OC values (15, 18, 21). In the study by Jung *et al*., s-OC levels in the TPTD group increased about 4-fold at 1st and 3rd months, with the differences from baseline being statistically different ($p<0.05$). In the control group, however, no significant differences were observed during the 3-month period (15). Similarly, the results in the study by Kim *et al*., showed that during 6-month period s-OC values increased up to 2.5-fold, while the non-TPTD group did not show any significant difference (18). In a multivariate analysis, including age, BMI, and duration of BP usage, the difference between TPTD and non-TPTD was significant ($p<0.05$). A study by Kwon *et al*. stated that the s-OC values increased in all patients during follow-up times and there is a statistically significant difference between baseline and 2 months in the TPTD group. There was also a statistically significant difference between baseline and 3 months period, respectively $p<0.006$, $p<0.011$ (21).

Daily vs weekly TPTD injection

Only one study compared daily and weekly administration of TPTD injections (16). The results showed no significant changes in the clinical stage of BRONJ, with a moderate improvement in both groups. The difference in quantitative analysis of bone scintigraphy was not significant, as well as the percentage of bone formation in patients' osteolysis. However, the medians of the bone turnover markers P1NP and OC showed greater changes in the daily group compared to the weekly group (16).

PRF vs TPTD

Only one of the involved studies compared the effectiveness of TPTD with PRF treatment in BRONJ lesions (20). All of the patients in both groups showed complete resolution of BRONJ lesions. Although PRF treatment showed a faster complete resolution, no difference in the rate of complete resolution was found between the two groups.

DISCUSSION

This review analysed the existing literature evaluating the use of TPTD in the treatment of BRONJ, which is defined as a diffuse bone disease characterized by the presence of bone exposed to the oral cavity that does not heal within 8 weeks of observation and conventional treatment, in patients under or had taken BP therapy, with no history of radiation therapy in the head and neck region (6). The management of BRONJ remains a controversial topic, as the current consensus on treating BRONJ patients is based on the conservative approach, mainly focusing on symptomatic treatment. TPTDs are anabolic agents, that directly stimulate bone formation by having an ability to activate pre-existing osteoblasts, increased differentiation of lining cells, and reduced osteoblast apoptosis, followed by activation of osteoblast. The purpose of this review was to evaluate whether the additional TPTD administration for patients with BRONJ is an effective treatment modality.

A total of 8 studies were included in the qualitative synthesis. These articles included a total of 139 patients with patients' mean age being 75.47 years. Follow-up time ranged from 3 up to 26 months. The most used BP was alendronate (62.8% of the patients), followed by risedronate, minodronate, ibandronate, zoledronate, denosumab, pamidronate. Risedronate and minodronate contain a higher per-

centage of nitrogen compared to the most commonly used alendronate. Furthermore, these BPs exhibit a stronger suppressive activity on osteoclast and bone metabolism and may cause more difficult bone turnover activation (23).

This systematic review also evaluated the resolution of BRONJ lesions. Studies comparing BRONJ treatment with and without TPTD indicate that better results were observed in those groups that used TPTD, but only one of the two studies indicated that this difference was statistically significant (17, 18). One of those studies by Sim *et al*. (17) also evaluated bone qualities and it showed that after 52 weeks TPTD treatment was associated with an increased bone volume and a reduced defect size (p=0.017). Five studies (16-20, 22) reported TPTD therapy with administration of the medication up to six months. The longer administration of TPTDs might have bigger impact as reported by Kwon (21). However, due to high prices of TPTD, it might be an obstacle against its use in clinical practice for some of the patients (24). Despite evidence that a longer period of treatment with TPTD may lead to better results, the use of TPTD for more than 24 months is not recommended due to a theoretical risk of osteosarcoma (25). It is also mentioned that the approved dosage is 20 micrograms per day and patients should also be prescribed supplemental calcium and Vitamin D during the duration of the treatment (25). Study by Kim *et al*. stated that patients with higher baseline serum 25-hydroxyvitamin D (25 (OH)D) levels showed better clinical therapeutic outcomes with TPTD and concluded that subjects with optimal serum vitamin D concentrations seemed to reap the maximum therapeutic effects of TPTD (18). Almost all the studies incorporated the use of serological parameters as the marker of bone formation/resorption. Following markers were used: s-CTX (serum cross-linked C-telopeptide of type I collagen), s-OC (serum osteocalcin), PINP (procollagen type I N-propeptide), 25 (OH)D (25-hydroxyvitamin D), BAP (bone-specific alkaline phosphatase) (15, 16, 18, 21, 22). Most of the studies found an increase in biomarkers between measuring at the baseline and posttreatment (15, 16, 18, 21). In addition, no significant link between the dynamic changes of the markers (BAP and CTX) and clinical findings were found, therefore they should be used with precautions to predict clinical outcomes (22). K. M. Kim *et al*. evaluated different bone turnover markers and concluded that only 25 (OH)D levels revealed a significant influence on the effect of treatment with teriparatide (18). Due to controversial findings regarding the clinical significance of biomarkers, more studies are needed to establish conclusions.

This review also included one study that compared the PRF and TPTD treatments of BRONJ lesions (20). Despite the small number of patients, BRONJ lesion treatment using PRF showed a faster complete resolution, however, no difference in the rate of a complete resolution was found between the groups, as all patients reached a complete resolution. A recent review by Fortunato *et al*. concluded that the application of autologous platelet concentrates (APCs) may be helpful in the treatment and prevention of BRONJ because of their local immunomodulatory properties and possible promotion of angiogenesis and tissue healing by platelet factors (27). However, there is very limited evidence on this topic, so additional studies are needed to find out which treatment is more effective.

Increased incidence of neoplasia is reported in an animal study with TPTD therapy by Vahle *et al*. (28) However, the higher doses and longer therapy was used on animals compared to human studies.

This review provides evidence for the potential benefits of additional TPTD administration for patients with BRONJ being an effective treatment modality. However, studies with larger samples of patients are needed to assess TPTD effectiveness, provide a protocol and show strong evidence about the efficiency of this treatment.

STATEMENT OF CONFLICTS OF INTEREST

The authors state no conflict of interest.

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