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REVIEW ARTICLE

Tetracycline impregnated bone grafts in the management of *peri*-implantitis and guided bone regeneration around dental implants: A systematic review

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KEYWORDS

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Bone regeneration;
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Peri-implantitis;
Tetracycline

Abstract *Background:* Rehabilitation of dental arches with the help of dental implants has been revolutionary and a significant part of research is devoted to increasing its success rate. One of the most common causes of failure of dental implants is *peri*-implantitis caused due to microbial invasion. Newer strategies are being adapted for the treatment of *peri*-implantits and recent surgical management with the help of antibiotic-impregnated bone grafts shows a promising future.

Aim and objectives: This study aimed to test the efficacy of bone grafts incorporating tetracycline and its derivatives in the treatment of *peri*-implantits and guided bone regeneration with the estimation of clinical and radiographic parameters.

Methods: A thorough search was made on eminent databases such as PubMed, Embase, Scopus, and Cochrane Library database for published literature on tetracycline impregnated bone grafts used either in the management of *peri*-implantitis or for guided bone regeneration around dental implants.The measures of outcome were clinical attachment loss or probing depth around dental implants and radiographic bone height.

Abbreviations: PD, Probing Depths; CAL, Clinical Attachment Loss

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Results: Nine potentially eligible full-text published articles including case reports, case series, observational studies, and randomized controlled trials were selected for review. Most of the studies reviewed; reported a reduction in probing depth and an increase in bone height and density after placement of tetracycline bone grafts around the dental implant.

Conclusion: The incorporation of tetracycline into the bone grafts shows promising results as an agent of local delivery around dental implants in the management of *peri*-implantitis and for guided bone regeneration. Future trials are required to produce a body of evidence and to facilitate the translation of this procedure into clinical practice.

Contents

1. Introduction

Dental implants remain a mainstream treatment for the rehabilitation of partial and completely edentulous arches among patients owing to their aesthetic as well as functional properties, longevity, and high success rate. Although the success rate of dental implants is high, early or late failures of implants are inevitable in some cases. The *peri*-implant bone volume and density are important factors that decide the overall outcome of dental implants (Steigenga et al., 2003). Furthermore, supportive measures such as regular professional biofilm removal at both implants and teeth also influence their long-term survival (Roccuzzo et al.,2018). *peri*-implantitis is a site-specific condition which is characterized by inflammation in the *peri*-implant mucosa and progressive loss of supporting bone structures. It is reported to be one of the commonest causes of implant failure (Stacchi et al., 2021).

Various non-surgical and surgical methods have been proposed for the management of *peri*-implantitis. Local mechanical debridement and surface decontamination using chemicals such as chlorhexidine, hydrogen peroxide, and citric acid have been tried as non-surgical methods. Antibiotic solutions such as that of tetracycline have also been utilized for the decontamination of implant surfaces (Valderrama et al., 2013). Furthermore, surgical modalities include bone augmentation using various bone grafts with or without biomembranes, and open-flap debridement techniques (Prathapachandran et al., 2012). Micro-invasive approaches such as videoscope-assisted surgeries and use of modified flap designs have also shown favourable results (Montero et al., 2022). The management of *peri*-implantitis usually involves a combination of both surgical and non-surgical strategies and one particular method cannot be credited as the most effective.

Bone grafts are generally recommended for guided bone regeneration around dental implants either after immediate placement or as a part of the management strategy in *peri*-implantitis. Long-term survival of dental implants and significant clinical changes have been observed in implants supplemented with deproteinized bovine bone mineral (Roccuzzo et al., 2017; Roccuzzo et al., 2020; Roccuzzo et al., 2021). Local delivery of antibiotics through bone grafts, biomembranes, concentrated microspheres, and local ointments offer great potential in the management of the condition. The local action of antibiotics is expected to prevent the growth of pathogenic microflora and provide optimum conditions for bone regeneration. Broad spectrum antibiotics such as tetracycline and its derivatives doxycycline, and minocycline have commonly been used for local delivery around dental implants (Mombelli et al., 2001;Passarelli et al., 2021).

The benefit of bone grafts in preserving connective tissue loss complemented with the local antimicrobial effect of antibiotics can prove to be an effective strategy for the management

of *peri*-implantitis and guided bone regeneration after immediate placement of dental implants, thus minimizing the incidence of implant failure. This systematic review was planned to produce pooled evidence after a qualitative analysis of this treatment modality in the management of *peri*-implantitis and for guided bone regeneration around dental implants.

2. Materials and methods

This systematic review was registered with PROSPERO under the registration number: CRD42022323779 and the reviewwas-carried out according to Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA) guidelines (Moher et al.,2009).

The research question was defined using PICO.

- Patient/Population (P): Patients requiring bone grafts around dental implants
- Intervention (I): Tetracycline impregnated bone grafts
- Comparison (C): Bone grafts without Antibiotics
- Outcomes (O): Bone height assessed through probing depth/Clinical attachment loss, Radiographs.

2.1. Search strategy

Literature search was carried out on databases such as PubMed, Embase, Scopus, Cochrane Library database, Web of Science, CTRI, LILACS, and DOAJ. Google Scholar search engine was ultilized to ensure an all-inclusive search. Additionally, the reference lists of selected studies were screened manually. No language restriction was imposed in the search. Only published articles were included in the review. All articles published from inception up till February 2022 were included. Keywords such as "bone graft", "antibiotics", "tetracycline", "dental implants", and "*peri*-implantitis" were used during the literature search either separately or in combination using boolean operators.

2.2. Study selection and eligibility criteria

Two reviewers independently screened the selected studies after the initial search to determine the relevance of each study. Any disagreement or discrepancy in the study between the two independent authors was resolved through discussion with other authors.

2.2.1. Inclusion criteria

1) Articles reporting the use of tetracycline-infused bone grafts around dental implants either for guided bone regeneration around dental implants or for the management of *peri*-implantitis.

2) Randomized controlled trials or observational study designs including cross-sectional, case-control, and cohort.

3) Case reports or case series reporting the use of tetracycline-impregnated bone grafts.

2.2.2. Exclusion criteria

1) Reviews, book chapters, personal opinions, letters to the editor, and conference proceedings.

2) Studies reporting the use of bone grafts for cases other than dental implants.

3) Studies reporting the use of antibiotics other than Tetracycline in the bone graft.

2.3. Data extraction

Two reviewers extracted all relevant information from the selected studies. Data about bibliographic information including the name of the first author, year of publication, country, study design, sample size, settings, site of defect, pre-treatment conditions (baseline characteristics), type of bone graft, the objective of placing the bone graft, antibiotic used and its dose, number of implants, type of implant, site of implant placement, follow-up period, outcome measures such as probing depth, and changes observed in bone height, radiographic or histopathologic findings, and postoperative complications were extracted. Any other relevant information found during data extraction was included. Disagreements between two independent reviewers were resolved by a third reviewer.

2.4. Quality assessment and risk of bias

The risk of bias was assessed by one reviewer while another checked the first assessment. Version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB 2) was used to assess the risk of bias for Randomized controlled trials (Sterne et al., 2019). ROBINS-I tools for observational or non-randomized studies of intervention (Sterne et al., 2016) and Joanna Briggs Institute Critical Appraisal Checklist was used for assessing the risk of bias for case reports and cohort studies (Moola et al., 2017).

2.5. Measures of outcome

Two primary outcomes, pocket depth or clinical attachment loss whichever was recorded in the study, and changes observed in bone height either radiographically or through other techniques were studied. Additional parameters such as clinical improvement in the patient's condition, postoperative complications, and follow-up period were also assessed.

3. Results

3.1. Study identification

The search strategy was performed by the PRISMA guidelines and has been summarized in the figure. [FIGURE 1]After an extensive search of various databases as described earlier, 70 articles were identified initially. Removal of duplicates and full-text screening further reduced the number of articles to 18 which were checked for eligibility criteria. Finally, 9 potentially eligible full-text published articles were selected for review (Deporter et al., 2001; Büchter et al, 2004; Park et al., 2004; Alghamdi et al., 2012; Park et al., 2012; Bhatavadekar et al., 2021; Philippart et al., 2003; Mercado et al., 2018; Emanuel et al., 2020).

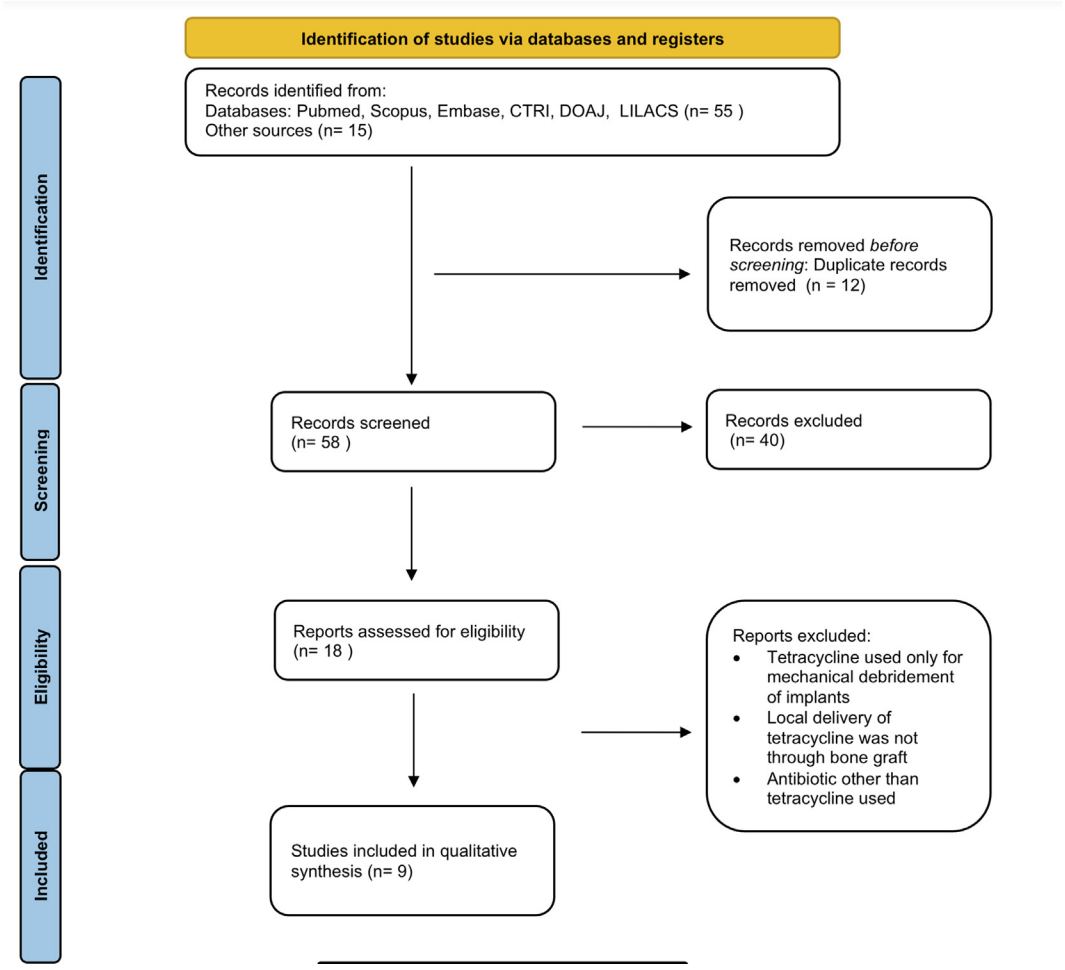

Fig. 1 PRISMA flowchart for search strategy.

3.2. Study characteristics

Six case reports or series (Deporter et al., 2001; Büchter et al, 2004; Park et al., 2004; Alghamdi et al., 2012; Park et al., 2012; Bhatavadekar et al., 2021) and one each observational non-ran domized-study-of-intervention (Philippart et al., 2003), cohort study (Mercado et al., 2018), and randomized controlled trial were identified (Emanuel et al., 2020). The total number of patients involved was 80, and the total number of implants placed was 150. The antibiotics infused into the bone graft were tetracycline, doxycycline, and minocycline. The included studies utilized antibiotic-impregnated bone grafts, either for the management of *peri*-implantitis or for maxillary sinus floor augmentation after implant placement. The primary outcome measures in the studies were probing depth and/or clinical attachment level, and changes in bone height level which were assessed through radiographs.A detailed description of the study protocol [TABLE 1], and its outcomes [TABLE 2] has been depicted in the tables.

Complete regeneration of alveolar bone height in studies was reported at the end of five or six months following the surgical treatment (Büchter et al, 2004; Bhatavadekar et al., 2021). An increase in bone height after bone graft placement was seen across a few other studies, followed by crestal bone loss and no further bone loss during long-term follow-up visits (Alghamdi et al., 2012;Mercado et al., 2018). Reduction in probing depth and/or clinical attachment loss with the use of bone grafts after five or six months of surgery was observed across all studies included in the review except for the study by Park et al. (2004) and Philippart et al. (2003) where probing depth or clinical attachment loss was not assessed. Histopathological analysis of newly formed bone was done by only one study where they found vascularised connective tissue regeneration with lamellar bone spicules, and osteocytes surrounded by osteoblasts at a follow-up period of 6 months (Deporter et al., 2001). Most studies had a follow-up period of around 1 year. However, it ranged from 4.5 months up to 36 months across the studies with the longest follow-up period noted in the study by Philippart et al (2003).Complications after bone-graft surgery or post-implant placement were not reported in any study.

3.3. Quality assessment

The overall risk of bias for the non-randomized observational study of intervention (Philippart et al., 2003) was calculated to be low using the ROBINS I tool,and the randomized controlled trial (Emanuel et al., 2020) assessed by the RoB2 tool was found to have some concerns concerning the randomization process, deviation from the intended outcome, and mea-

Table 1 Study characteristics: Design and Method.

Author	Study design	Sample size	Bone graft	Antibiotic used	Dosage of antibiotics	Number of implants
Deporter et al., 2001	Case report	1	Deprotenized freeze-dried bone allograft premixed with Antibiotic	Tetracycline	50 mg/ml	3
Philippart et al., 2003	Observational	18	Autogenous calvarial particulate bone graft, recombinant human tissue factor, platelet rich plasma	Minocycline	100 µg/ mL	58
Büchter et al, 2004	Case report	1	Autogenous bone graft, biodegradable polymer that delivered antibiotic	Doxycycline	Not mentioned	2
Park et al., 2004	Case Series	2	Demineralized freeze-dried bone allograft mixed with Antibiotic	Tetracycline	250 mg	2
AlGhamdi et al., 2012	Case Series	11	Bovine Bone, Calcium sulphate with Antibiotic	Doxycycline	50 mg	18
Park et al., 2012	Case report	1	Deproteinised bovine bone with antibiotic	Tetracycline	4:1 ratio by volume	3
Mercado et al., 2018	Prospective Cohort	30	Deproteinized bovine bone mineral with 10 % collagen, Enamel Matrix Derivative and antibiotic	Doxycycline	100 mg	30
Emanuel et al., 2020	RCT	27 (14: D-PLEX500 + 13 control, no graft)	D-PLEX500: Beta tricalcium phosphate granules, poly (lactic-*co*-glycolic acid), lipids, broad-spectrum antibiotic	Doxycycline	56 mg per 10 g vial	(18 in intervention group + 14 in control group)
Bhatavadekar et al., 2021	Case series	2	Deproteinized bovine bone mineral with 10 % porcine collagen in a block form, soaked in antibiotic.	Tetracycline	400 mg in 1 ml saline	2

surement of outcome. [FIGURE 2] The quality of case reports (Deporter et al., 2001; Büchter et al, 2004; Park et al., 2004; Alghamdi et al., 2012; Park et al., 2012; Bhatavadekar et al., 2021) [FIGURE 3] and cohort study (Mercado et al., 2018) [FIGURE 4] assessed through the JBI critical appraisal checklist are shown in the figures.

4. Discussion

Peri-implantitis is a pathological condition involving soft and hard tissues around the dental implants, characterized by inflammation in the *peri*-implant mucosa and progressive loss of supporting bone structures (Schwarz et al., 2018). It has an anaerobic polymicrobial etiology where the lesions harbour bacteria that are not a part of the typical periodontopathic microbiota. In addition to the conventional scaling and root planing, a treatment approach involving local delivery of antimicrobials has shown promising results as described in various studies (Mombelli et al., 2001; Passarelli et al., 2021). Toledanoet al (2021) in their systematic review discuss the efficacy of antibiotics in the reduction of probing depths around dental implants and recommend the use of local antibiotics to treat *peri*-implantitis. Local delivery of antimicrobials can be accomplished either through rinses such as Chlorhexidine or by antibiotics infused into the bone graft or the bio membrane around the dental implant (Smeets et al., 2014). Tetracycline and doxycycline are the most commonly used antibiotics in the treatment of failing implants through local delivery because of their broad spectrum of action (Büchter et al., 2004). Other commonly used antimicrobial delivery systems include Tetracycline fibres, Metronidazole gel, Chlorhexidine chip, Minocycline gel, and Doxycycline polymer among many others (Pattanshetti et al., 2016).

The primary outcome measures selected for the review were probing depths (PD) or clinical attachment loss (CAL). Probing depth has been included by the American Academy of Periodontology as a defining quantitative parameter for periodontal health with a value of 3 mm or less for a clinically healthy sulcus. Pocket probing is therefore an important diagnostic modality for the assessment of periodontal status and the evaluation of periodontal therapy (Salvi et al., 2004). However, Lekholm et al (1986) in their study aftera long-term follow-up of 7.6 years have concluded that bleeding of *peri*-implant tissues and deep pockets are not necessarily related to crestal bone loss, the presence of a pathogenic microflora or histologic changes indicative for signs of periodontitis. Additionally, Coli et al (2017) in their review have stated on the unreliability of probing depth as an outcome to evaluate loss of bone around the implant in *peri*-implantitis. In our review, most studies used probing depth as an outcome measure to determine the treatment progression at various months of follow-up. We recommend more speculations around parameters that can standardize defining the *peri*-implantitis condition and treatment outcomes in general.

Philippart et al (2003) and Park et al (2004) did not study PD/ CAL in their studies. Instead, they reported radiographic changes in bone height and density. Philippart et al (2003) observed an increase in bone height during the first 6 months which regressed to normal heights after 2 years. Park et al (2004) reported an increase in bone density in the radiographs at 5-month follow-up of the patients. However other studies have also shown that along with a reduction in probing depths, there has been an eventual increase in bone height and/ or density at further follow up visits. Although most studies reported an increase in bone height after treatment with antibiotic bone grafts, the radiographic technique used to evaluate changes in

Table 2 Study characteristics: Measures of outcome and Results.

Author	Outcome measures	Follow up	Mean difference: Probing depth/ CAL	Changes in bone height
Deporter et al., 2001	Probing Depth, Radiographic assessment of bone	6 months, 1 year, 2 years	Resolution of defect during follow up	Stable at 2 years
Philippart et al., 2003	Histological Analysis, Bone Scintigraphy	8 months	Not assessed	Maximum reached after 6 months and slowly decreased to a normal level after more than 2 years
Büchter et al, 2004	Probing Depth, Clinical Attachment Level, Radiographic assessment of bone	5 months	Mesial: 11 to 3 mm, Median: 10 to 3 mm, Distal:8 to 4 mm Palatinal: 9 to 4 mm; CAL: 3 mm decrease after treatment	Regeneration seen radiographically at 5 months
Park et al., 2004	Radiographic assessment of bone	6 months	Not assessed	Increase in radiograph bone density at 5 months
AlGhamdi et al., 2012	Probing Depth, Clinical Attachment Level, Radiographic assessment of bone	6 months, 12 months, 30 months	Range: 3 to 5 mm at 12 months	Baseline includes average 3.15 mm early progressive bone loss after implant placement.Post placement increase at 6 months (complete bone restored). Loss at 12 months (avg 1.3 mm crestal). No further loss at follow-up visits
Park et al., 2012	Radiographic assessment of bone	4.5 months, 6 months	Baseline: 8 mm Final: 5 mm	Increased radio-opacity
Mercado et al., 2018	Pocket Probing depth, Mucosal Recession, Buccal keratinized tissue, Radiographic assessment of bone	12, 24, 36 month	Baseline: 8.9 ± 1.9 mm.At 12,24,36 months: 3.55 ± 0.50 mm.	Radiographic measurements of Bone loss(mm) Baseline: 6.92 ± 1.26. 12 months: 2.85 ± 0.73. 24 months: 2.62 ± 0.80. 36 months: 2.60 ± 0.73.
Emanuel et al., 2020	Pocket probing depth, Clinical attachment level, Bleeding on probing, Mucosal recession, Radiographic assessment of bone	6, 12 month	Mean difference: 6 months: [test: 2.33 _ + 1. 84; control: 2.07 _ + 2.01]; 12 months: [test: 2.88 _ + 1.52; control: 1.64 _ + 2.13)	2 mm increase at both 6, and 12 months
Bhatavadekar et al., 2021	Probing Depth Radiographic assessment of bone	5 months	Probing depth: Case 1: 6 mm to 4 mm; Case 2: 7 mm to 4 mm	Baseline: 40 % loss, complete regeneration at 6th month

bone height has its demerits. Bone loss is evident on radiographs only after a significant amount of demineralization. Moreover, the difference between clinical alveolar crest height and radiographic crest height can vary from 0 to 1.6 mm based on the radiographic beam angulation and therefore is less reliable (Regan et al., 1963). Interpretation of radiographic images also pose significant inter and intra-observer variability due to various factors such as quality of image, or expertise of interpreter (Afrashtehfar et al., 2020).

Several studies in this review used intraoral periapical radiographic images to assess bone height subjectively based on the increase in radiopacity or increase in vertical or horizontal bone height without any measurements or quantification. Bone Scintigraphy, a functional imaging method based on the intensity ofradioisotope uptake by the bone, was used by Philippart et al., (2003) where radioisotopic images of the skull were obtained. However, no significant differences have been found in assessment of healing time between Magnetic Resonance Imaging and Bone Scintigraphy according to previous reports (Dobrindt et al., 2012). Recent advanced techniques such as Computer-Assisted Densitometric Image Analysis System (CADIA) has been shown to be more reliable than conventional radiographic techniques (Zaki et al., 2015). Computerized approaches for recording alveolar crest height are recommended and specific guidelines are required to record bone height around dental implants to facilitate standardization across studies.

Most of the studies (6 out of 9, 66.7 %) assessed the primary/secondary outcome measures till 1 year post op follow up, earliest being checked at 4.5 months by Park et al (2012). However, 3 studies assessed the PDs, for more than 1 year. Mercado et al (2018) followed the cases up for 36 months. This provides us a wide spectrum of results across a large timeframe for the review. As noticed in other studies, the initial improvement in the condition of the patient is generally noted in this period, while a regressive phase follows after which more stable results are obtained at the end of nearly 24 months or more. Similar review has been shared by Preus et al (2014).

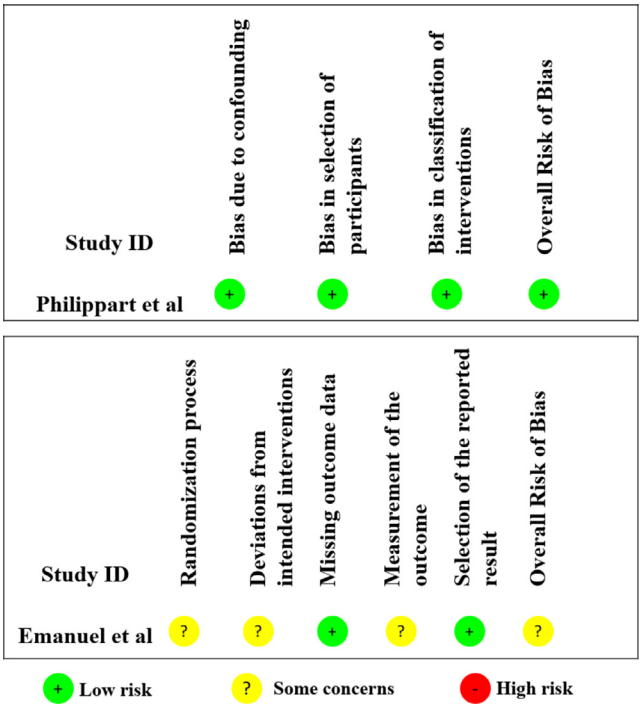

Fig. 2 Risk of Bias evaluation for non-randomized observational study of intervention using ROBINS I tool.

A minimum follow up of two years post regenerative surgery is recommended for obtaining a more sustained result, along with 4–6 weeks follow up after implant placement for detection and management of early implant failure.

All included studies used tetracycline group of antibiotics for local delivery. 4 studies used doxycycline (44.4 %), 4 used tetracycline (44.4 %), and 1 (11.1 %) study used minocycline in their bone grafts. The rationale behind incorporating an antibiotic in the bone graft for local delivery is to reduce the chances of postoperative infection, and inhibit the pathogenic microflora which could interfere in the bone healing process. Tetracyclines concentrate in periodontal tissues and inhibit the growth of *Aggregatibacter actinomycetemcomitans*. Additionally, they exert an anti-collagenase effect that can inhibit tissue destruction, thushelping bone regeneration (Newman et al., 2018). Moreover, tetracycline as a local antibiotic infused in the bone graft has shown to increase the osteogenic potential of the bone graft by inhibition of matrix metalloproteinase I, thereby reducing bone resorption (Kline et al., 1995). This is one of the important reasons why tetracyclines are widely utilized as antibiotics in anti-infective therapy in the periodontium.

Many studies have used broad spectrum antibiotics prophylactically through systemic oral routes for prevention of secondary infections after implant placement and bone augmentation procedures. However, the evidence behind the efficacy of such regime is limited (Klingeet al., 2020). Such practices could lead to development of antimicrobial resistance which is considered as a global threat to humanity. The use of

JBI Checklist	Andre Buchter et al	AlGhamdi et al	Park et al	Deporter et al	Bhatavadekar et al	Beom Park et al
1. Were patient's demographic characteristics clearly described?	No	Yes	No	Yes	No	No
2. Was the patient's history clearly described and presented as a timeline?	No	No	No	No	No	No
3. Was the current clinical condition of the patient on presentation clearly described?	No	No	Yes	Yes	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
7. Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Yes	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes

Fig. 3 Critical appraisal of the case reports through JBI checklist.

JBI APPRAISAL FOR COHORT STUDY	Mercado et al
1. Were the two groups similar and recruited from the same population?	Unclear
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes
3. Was the exposure measured in a valid and reliable way?	Yes
4. Were confounding factors identified?	No
5. Were strategies to deal with confounding factors stated?	No
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes
7. Were the outcomes measured in a valid and reliable way?	Yes
8. Was the follow up time reported and sufficient to be long eNough for outcomes to occur?	Yes
9. Was follow up complete, and if Not, were the reasons to loss to follow up described and explored?	Yes
10. Were strategies to address incomplete follow up utilized?	Not applicable
11. Was appropriate statistical analysis used?	Yes

Fig. 4 Critical appraisal of cohort study through JBI checklist.

antibiotic infusions through bone grafts offers an optimum choice for the prevention of antimicrobial resistance by targeted delivery at the site of dental implant. The dosage of antibiotics infused into the bone graft could possibly influence healing of the soft and hard tissues. Although all studies mention the dosage of tetracycline used, none of them have compared the bone regeneration potential around dental implants on altering the dosage. Moreover, no information regarding the rationale behind selection of that particular dose used in the grafts has been shared. Therefore, future studies could compare the different doses of tetracycline such that a standard dose of Tetracycline to be used in bone graft is established.

Out of the nine studies included in the systematic review, six (66.7 %) were case reports/ case series, which forms level 4 of level of evidence for therapeutic studies (Burns et al., 2011). There was only one randomized controlled trial that could be retrieved using the search keywords across all the databases searched. This in itself emphasizes the need of higher evidences in this prospect.

Limitations: The sources of heterogeneity across studies include the usage of other biomaterials along with the bone graft such as recombinant human tissue factor, platelet rich plasma, and Enamel Matrix Derivative in some studies. Therefore the results indicating bone regeneration could have been the conjugated effect of the growth factors from PRP, recombinant human tissue factor and tetracycline. Similarly Enamel matrix derivative, known for its osteoconducive properties could supersede the role of antibiotic in the bone graft. There was subjectivity in reporting of outcomes in certain studies which made performing *meta*-analysis difficult. The review included only published studies which could lead to overestimation of positive results obtained in the review.

5. Conclusion

The review discusses the potential benefits of local delivery of tetracycline with bone grafts for optimum bone regeneration around dental implants and for the management of *peri*-implantitis through local antimicrobial action. Although the findings across studies included in the review support the usage of antibiotics for local delivery through bone grafts, more randomized controlled trials are recommended to establish its efficacy around dental implants inguided bone regeneration and management of *peri*-implantitis. Parallel groups with plain bone grafts as control and tetracycline-impregnated grafts as intervention, a long-term follow up period, and more reliable measures of outcome with quantificationof radiographic bone height using grids, and three-dimensional radiographs are suggested.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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