J Den Res Pract 2020; 2(1): 10.

Journal of
Dental Research and Practice

Review

Porous Titanium Granules (PTGs) for Treatment of Peri-implant Osseous Defects

Muataz Osman[1*], Hugo Pinto[2], Kevin Seymour[2]

[1]Periodontology Department, University of Manchester, Periodontology Department faculty of dentistry Benghazi university, Restorative department faculty of dentistry , Libyan international medical university LIMU

[2]Division of Dentistry, University of Manchester, Manchester, United Kingdom

[*]Correspondence should be addressed to Osman M, Division of dentistry, School of Medical Sciences, University of Manchester , Manchester, United Kingdom; Tel +44 7478466341; E-mail muataz.osman@postgrad.manchester.ac.uk

Received 1 May 2020 Accepted 13 May 2020

ABSTRACT

A large number of different treatment protocols, materials and techniques have been suggested for the treatment of peri-implantitis, yet there is no agreement between specialists in this field regarding the most effective regenerative intervention which can lead to complete resolution of infra-bony defects around implants or to arrest the progression of peri-implantitis.

The aim of this review was to evaluate the available evidence in the literature about the benefit of using porous titaniu m granules (PTGs) as a reconstructive approach for treating infra-bony defects caused by peri-implantitis.

The study searched PubMed, Ovid MEDLINE and EMBASE databases until January 2019. Animal and clinical human studies that had reported the use of PTGs for the regenerative treatment of peri-implantitis were included according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The initial electronic and manual search obtained 20 citations. After screening and determination of eligibility, 10 articles were included in the review. Results from animal and human studies, including two randomized controlled trials are too heterogeneous to allow meta-analysis. Results show that the use of PTGs for the treatment of peri-implant osseous defects can yield predictable results, although the evidence is scarce.

According to the available materials one can suggest that using PTGs for treating peri-implant osseous defects could be a viable option among other available techniques. However, in case of recurrent peri-implantitis for the treated sites, a larger defect can be the result.

Keywords: Porous titanium granule (PTGs), Peri-implantitis, Peri-implant bony defect, Bone regeneration, Regenerative treatment of peri-implantitis.

INTRODUCTION

Over the last few decades, the use of dental implants for replacing missing teeth has become the treatment of choice when compared to conventional fixed and removable prostheses. With survival rates approaching 95%, implant therapy has become a successful treatment option in medical sciences, [1].

Despite its popularity among patients worldwide and its high success rate, dental implant therapy is associated with a steady increase in the development of biologic and technical complications [2]. The most common complication associated with implant treatment is peri-implantitis, which is clinically defined as a pathological condition occurring in the tissues around dental implants, characterized by inflammation in the peri-implant mucosa and progressive loss of supporting bone [3]. The prevalence of peri-implantitis has been reported to be in the range of 1.4% to 53.3% and the reason for this discrepancy, according to the literature, are the different definitions of peri-implantitis used by different researchers [4].

The main aim of peri-implantitis treatment is to arrest the progression of the disease and at the same time keep the dental implant in function with surrounding healthy soft and hard tissues. Peri-implant bony defects can be treated with either non-surgical or surgical (resective or regenerative) techniques. Bone tissue regeneration is possible in selected peri-implant bony defects of functioning implants if appropriate surgical techniques are used and the aetiological cause is fully eliminated [5]. In a recent systematic review and meta-analysis investigating the treatment outcomes of surgical management of peri-implantitis, the authors [6] concluded that four main surgical approaches have been identified for the treatment of peri-implantitis, which include open flap debridement (OFD), resective procedures,

regeneration with bone grafting materials and substitutes as well as guided bone regeneration (GBR). The authors have further revealed that, in short-term follow up periods, these procedures resulted in an estimated 2 to 3 mm probing pocket depth reduction, equivalent to 30% to 50% of the initial pocket depth. In addition, a mean of 2 mm of radiographic bone fill was achieved in regenerative procedures [6].

A wide range of bone grafting materials have been used in the treatment of peri-implantitis. The most recent meta-analysis reviewing surgical regenerative treatment of peri-implantitis concluded that all included studies resulted in clinical improvement following regenerative therapy; however, there was a lack of scientific evidence in the available literature regarding the superiority of one regenerative approach over the other or over non-regenerative surgical therapy [5].

In the last decade, the use of porous titanium granules (PTGs) has been introduced as a reconstructive approach for the treatment of peri-implant osseous defects. PTGs were initially used in orthopaedics for the stabilization of hip prostheses to enhance bone regeneration [7,8]. Since then, several studies have been conducted to investigate if there is any benefit of using PTGs for the treatment of peri-implant osseous defects.

Would it be worth a brief sentence about the basics of PTG therapy here?

The purpose of this review is to systematically evaluate the literature on the use of PTGs as a surgical reconstructive approach for the treatment of peri-implant osseous defects.

MATERIALS AND METHODS

The following focus question was developed according to the population, intervention, comparison, and outcome (PICO) study design:

What is the benefit of using (PTGs) as a treatment option in the regeneration of infra-bony osseous defects caused by peri-implantitis, when compared with other materials?

The search strategy incorporated examinations of electronic databases, supplemented by hand searches. A search of electronic databases, including PubMed, Ovid MEDLINE and EMBASE was carried out for relevant studies published in English language until January 2019. Additionally, the authors carried out a hand search performed in dental and implant-related journals limited to English language for the same period. A hand search of the reference lists in the articles retrieved was also carried out to source additional relevant publications and to improve the sensitivity of the search.

The keywords used in the search of the selected electronic databases were the following: “peri-implantitis” OR “periimplantitis” OR “peri-implant” OR “periimplant” or (“dental implant” AND “failure”) AND “surgery” OR “surgical” OR “regeneration” OR “regenerative” OR “treatment” OR “therapy” OR “bone graft” OR “bone substitute” AND “porous titanium granules” OR “titanium granules” OR “PTG”. The choice of keywords was intended to be extensive, to collect as much relevant data as possible.

The resulting articles were independently subjected to clear inclusion and exclusion criteria by two independent reviewers MO & HP. Reviewers compared decisions and resolved differences through discussion, consulting a third party KS when consensus could not be reached. Following the initial literature search, all article titles were screened to eliminate irrelevant publications, considering the exclusion criteria. In the subsequent stage, studies were excluded based on data obtained from screening the abstracts. The final step of screening involved reading the full texts to confirm each study’s eligibility, based on the inclusion criteria.

Inclusion criteria

The review included all animal, in vitro and human prospective and retrospective follow-up studies as well as clinical trials, cohort studies, case-control studies, and case series on surgical regenerative treatment of peri-implantitis using PGT, published in English untilJanuary 2019.

Exclusion criteria

Not enough information regarding the selected topic;
No access to the title and abstract in English language.

Assessment of risk of bias was undertaken independently, and in duplicate by the two authors MO and HP during the data extraction process. The heterogeneity of the studies did not allow meta-analysis and the results have been presented as a descriptive review.

RESULTS

The primary electronic and manual search resulted in 20 citations. After screening titles and abstracts and the application of the inclusion and exclusion criteria 10 publications were included in the review, including 2 pre-clinical trials and 8 studies in humans. The characteristics of the pre-clinical and human studies are presented in tables 1 and 2, respectively.

The 1st animal study, [9] aimed to investigate the osteoconductive ability and biological performance of two types of PTGs (metallic and white) what are metallic and white? The reader will want to know!, when used as a bone substitute for the treatment of osseous defects prepared adjacent to titanium implants in rabbit tibias. On visual inspection, PTGs were well-integrated in the healed cortical bone. The control (no graft used) sites appeared as an open defect with only partial cortical bone closure. Radiographically, a statistically significant difference in new bone formation was detected by the micro-CT with more bone seen in the PTGs groups than in the control. No significant difference was found between the two titanium groups. The authors suggested that PTGs provide osteoconductive scaffolding that can be used safely adjacent to titanium dental implants [9].

In the 2nd animal study carried out in dogs a significant increase in the defect infill with newly formed bone in all test sites with both Bio-Oss® and PTGs groups when compared with the control sites (no graft) in the 4th and 8th week evaluations was demonstrated. Also, there were significant

increases in the percentage of the defect infill in all test and control sites between 4 and 8 weeks [10]. The authors have concluded that both test materials resulted in defect infill with newly formed bone; however, the bone-to-implant contact was only increased in the Bio-Oss® grafted sites and these findings suggest that the healing of peri-implant defects is not only influenced by the osteoconductivity but also by the surface characteristics and mechanical properties of the grafting materials [10].

The included human studies reported outcomes were the presence of complications during the healing, changes in clinical parameters such as bleeding on probing (BOP), probing pocket depth (PPD), radiographic infill of the defects, as well as histological analysis.

No signs of inflammation during the healing period were described by the two case reports [11, 12]. No post-operative complications were reported by the RCT [13]. A retrospective cohort study showed bleeding and suppuration during the healing after treatment with PTGs in 2 out of 18 cases [14].

In the RCT by Wohlfahrt, the result showed reduction in probing pocket depth, with no statistical significant difference between test (PTGs) and control (no graft) after 12 months follow up [13]. No significant difference in terms of PPD and BOP reduction could be found between the test (PTGs) and the control group (no graft) in a multicentre RCT [15]. When PTGs and xenograft were compared for the treatment of peri-implant defects in a RCT, there were no statistical significant differences reported in terms of PPD and BOP reduction [16].

One case report showed radiographic reduction in the defect depth without complete resolution of the defect, whilst the other case report showed complete resolution of the defect, radiographically [12]. A RCT conducted in 32 patients showed statistical significant differences in terms of radiographic infill of the defect when PTGs were used in comparison with no graft (57% and 18% respectively, $p<0,001$) [13]. However, these results had not remained stable at the 7 year follow-up, showing a reduction in the defect infill in both study groups [17]. A multicentre RCT showed significantly higher defect infill and marginal bone gain in the PTGs treated sites compared with the control group [15]. A RCT comparing PTG (test) and xenograft (control) showed higher bone infill values in the test group at 6 months evaluation with statistical significance [16].

Histological analysis carried out in a case report showed that PTGs were well-integrated in woven as well as lamellar bone zones, with areas of re-osseointegration, however, areas with fibrous tissue between the implant and the bone were also identified [12].

A study carried out with the same population as a previous study [13] concluded that the surgical therapy of peri-implantitis can induce a reduction in factors involved in the regulation of extracellular matrix degradation and bone remodelling and that the reduced levels of MMP-8, insulin, IL-6 and osteprotegerin in peri-implant sulcus fluid were correlated with the clinical outcomes. However no difference between both test and control groups was found **(table 1 and 2)** [13].

Table 1: Brief Description of Pre-clinical Studies.

Authors/ Year	Study type/ Method	Study design	Follow-up Period	(n) of Subjects Included	(n) of Treated Defects	Surgical Treatment(s)	Outcome Measures	Conclusion
Wohlfahrt, et al. [9]	Animal study, rabbit tibia peri-implant osseous defects	Randomised, parallel-arm animal experiment	4 weeks	24 New Zealand rabbits	20 defects	Sham defects (8), metallic PTGs (8) and white (oxidised) PTGs (4)	New bone within the volume of interest (VOI), osseous formation in the bone marrow compartment, horizontal and vertical osseous regeneration.	Both metallic and white PTGs are osteoconductive materials and can be used safely adjacent to titanium implants.
Lee, et al. [10]	Animal histological study	Randomised 3-arm pre-clinical trial	4 and 8 weeks	5 dogs	30 defects (10 PTGs, 10 Bio-Oss, and 10 Sham defects)	Two test groups (PTGs and Bio-Oss) and one control sham group	Histological healing patterns of peri-implant defects, new bone formation in the defect, bone-to-implant contact, and the presence of blood vessels adjacent to the newly formed bone.	The results showed that healing pattern around dental implants could be affected by the surface/ mechanical properties of the grafting

								materials beside their osteocond uctivity.

OFD; open flap debridement, BOP; bleeding on probing, PTGs; porous titanium granules,

REC; recession, CAL; clinical attachment level, HO; hydrogen peroxide,

PPD; probing pocket depth, EDTA; ethylene diamine tetra acetic acid, PRF; platelet-rich fibrin.

Table 2: Brief description of human studies included in this review.

Authors/Year	Study type/ Method	Study design	Follow -up Period	(n) of Subjects Included	(n) of Treated Defects/ implants	Surgical Treatment(s)	Outcome Measures	Conclusion
Wohlfahrt, et al.[12]	Human histological and radiographi c study	Case report	12 months	1 female	1 defect	OFD, debridement with titanium curettes, 24% EDTA was used, cortical perforations were created, then PTGs were inserted and flap closure achieved.	Radiographic defect fill, scanning electron microscopy for re-osseointegrati on analysis and histological analysis for new bone formation.	The results justified further clinical testing of PTGs as a grafting material.
Wohlfahrt, et al.[12]	Human histological study with surgical re-entry.	Case report	6 months	1 female	1 defect	OFD, titanium brush was used for debridement, 3% HO was used and PTGs inserted.	Visual assessment of the defect by surgical re-entry.	Defect and implant surface debridement with titanium brush and 3% HO + reconstructio n with PTGs is a potential treatment option for treatment of narrow peri-implant osseous defects.
Wohlfahrt, et al.[13]	Human RCT	Prospecti ve, randomis ed, case-control, clinical study.	12 months	32 individual s	32 defects (16 test and 16 control)	Control; OFD, decontaminatio n with titanium curettes and 24% EDTA; Test; same as control+ PTGs	PPD, BOP, implant stability and radiographic defect fill	Defect deconstructio n with PTGs resulted in significantly better radiographic defect fill compared with OFD alone; however, this does not mean re-osseointegrat ion or osseointegrat ion of the titanium particles. Further, clinical parameters improved in both groups without differences demonstrate

								d between both groups.
Mijiritsky, et al. [14]	Human clinical study	Retrospective cohort study	Mean 7.5 months ± 3.9 (6 to 15)	16 individuals	18 implants	OFD, decontamination with tetracycline + PTGs and apically repositioning flap.	PPD, BOP, suppuration and radiographic evaluation to assess bone loss around the implants.	Using PTGs could be a viable option for treatment of peri-implantitis cases.
Jepsen K, et al. [15	Human clinical study	Prospective, randomised, case-control, clinical study.	12 months	32 individuals	32 defects (16 test and 16 control)	Control; OFD, decontamination with titanium curettes and 24% EDTA; Test; same as control+ PTGs	Peri-implant sulcus fluid bone marker levels for (MMP-8, IL-6, OPG, PTH, TNF-α, insulin, osteocalcin, leptin, and osteopontin)	Surgical management of peri-implantitis can induce reduction of some of the studied bone markers; however, no correlation was found between the change in bone levels and the disease resolution.
Guler, et al. [16]	Human Multicenter and Multinational RCT	Prospective multicenter, multinational randomised parallel-group clinical trial	12 months	63 patients	63 implants	Control; OFD, decontamination with titanium brush and HO (30); Test; same as control + PTGs (33)	PPD, BOP, suppuration, plaque scores and radiographic defect fill.	Similar clinical improvements were obtained from both treatment modalities, but significantly higher radiographic defect fill was observed in the PTGs group. There was no significant difference in terms of disease resolution.
Andersen, et al. [17]	Human clinical study	Parallel-group clinical trial	6 months	22 patients	35 implants	Test; OFD, granulation tissue removal with titanium curettes, decontamination with titanium brush + PTGs and PRF membrane; Control; OFD, granulation tissue removal with titanium curettes + xenograft, collagen membrane and PRF.	PPD, BOP, CAL, plaque index, gingival index, REC, and width of keratinized tissue.	Using PTGs might be more appropriate for surgical treatment of peri-implant osseous defects than xenograft due to their inert structure and providing mechanical support for increasing the implant surface area for osseointegration. Moreover, higher radiographic bone fill was observed in

								the PTGs group.
Wohlfahrt, et al. [48]	Long term evaluation of data from RCT	Long term evaluation of data from RCT	Mean 7.3 years (6.7 to 8)	12 patients	12 implants	Control; OFD, decontamination with titanium curettes and 24% EDTA; Test; same as control+ PTGs	PPD, BOP, implant stability and radiographic defect fill	The long-term clinical and radiographic outcomes of surgical treatment of peri-implantitis (with or without grafting materials) is unpredictable.
OFD; open flap debridement, BOP; bleeding on probing, PTGs; porous titanium granules, REC; recession, CAL; clinical attachment level, HO; hydrogen peroxide, PPD; probing pocket depth, EDTA; ethylene diamine tetra acetic acid, PRF; platelet-rich fibrin.								

DISCUSSION

The heterogeneity of the studies did not allow meta-analysis and the authors have decided to present the results as a narrative review divided into animal studies and human studies.

Peri-implantitis is a disease that occurs around dental implants which have been in function for a period of time. In a literature review regarding the prevalence of peri-implantitis [18], the authors have reported that peri-implantitis was found in 28% - 56% of subjects and in 12% - 43% of implant sites. All treatment options that have been proposed over the last few years for the management of peri-implantitis were based on the evidence available for the treatment of periodontitis [19]. However, there are clear differences between rough surfaced, screw root-formed dental implants and natural teeth in many aspects. It is of great importance for dental professionals to find ways to treat peri-implantitis and to regenerate the lost bone that occurs around implants due to peri-implant disease.

The ultimate goal of this treatment should be the achievement of re-osseointegration on the exposed implant surface. In this regard, several attempts have been made to determine a treatment protocol that could successfully accomplish this [19]. These attempts included conservative, resective and regenerative treatment in conjunction with various methods of additional surface decontamination and using different natural and synthetic grafting materials.

Animal studies

In a novel rabbit tibia model [9] investigated for the first time the osteoconductivity of PTGs in cortical bone and bone marrow. They further investigated whether PTGs could be used as a regenerative material in osseous defects adjacent to titanium implants. These granules have several features that make them good candidates to be used as a bone graft substitute around dental implants; they are made of the same material (titanium), provide immediate stability to the implant as well as permanent soft tissue support for better PI mucosal contour. However, the surface roughness and porosity of the granules could provide a treatment challenge if the material is exposed to the oral environment and gets infected.

Several surgical procedures and techniques for the treatment of peri-implantitis have been evaluated on both humans [6,20-30] and animals [31-40]. In many of these animal studies, it has been questioned if osseointegration or re-osseointegration in previously contaminated implant surface can be established.

In 2003, Schou and his research group have reported in animal studies [37-40] that re-osseointegration is possible but it depends on the implant surface characteristics. Their results showed almost complete bone regeneration and mean bone-to-implant (BTI) contact of 45%. Furthermore, a study [36] illustrated higher re-osseointegration amount around rough surface implants (84%) than that around machined surface counterparts (22%) after OFD in dogs.

Autogenous bone has been considered as the gold standard grafting material for a long time [41], and it is still recommended whenever possible. Various bone grafting materials and substitutes have been used to simplify the surgical procedure and eliminate the need for bone harvesting with increased potential risk of donor site morbidity [42,43]. For the last 25 years, particular attention has been paid to bovine-derived bone material (Bio-Oss®). Large number of studies have been published illustrating the important properties that this material has, including its bio-compatibility, osteoconductivity, and that it can be used as a scaffold for the ingrowth of the host cells.

The two included animal studies in this review [9,10] have shown almost similar results to those using other grafting materials such as autogenous [39,40] and bovine-based bone substitutes [37]. Wohlfahrt et al in 2010 have illustrated the bio-compatibility and potential osteoconductivity of the PTGs [9]. On the other hand, in their comparison between PTGs and Bio-Oss in dogs the authors concluded that both materials significantly enhanced the defect infill with newly formed bone to 85% and 86% for the PTGs and Bio-Oss respectively

[10]; however, bone-to-implant contact (BIC) was only significantly increased in defects grafted with Bio-Oss.

Human studies

In humans, few clinical studies have reported on the long-term results after treatment of peri-implantitis. In this regard, it has to be mentioned that the only true end point outcome for such therapies will be implant loss; however, most studies reported clinical and sub-clinical surrogates (being a measure of effect of a specific therapy that could be correlated with a real clinical endpoint [44,45]) outcomes for both the disease state and the true results of the investigated treatment or technique [46].

No adverse effects were mentioned in any of the included human or animal studies in this review beyond what is considered normal for any other surgical procedure in the mouth. None of the included patients reported any pain, discoloration of the surrounded mucosa or loose particles of the grafting material and this was observed in every single study included in this review.

The mean reductions in PPD using PTGs in the included studies [13,15,16] were about 2 mm, 2.8 mm, and 1.5 mm respectively which are, to a certain extent, comparable with other studies treating peri-implantitis with or without using grafting materials, as reported in recent systematic reviews [5,21]. More recently, in a long-term (7 years) follow-up clinical study on surgical management of peri-implantitis including OFD and implantoplasty combined with two different decontamination techniques and regeneration with natural bone mineral and GBR with a collagen membrane, the authors reported a CAL gain of 2.06 mm and 2.76 mm [28]. Moreover, the mean PPD reduction at the deepest point mentioned after 7 years when using PTGs [17] (4.3 mm ± 3.5) was in agreement with other study using bone substitute with or without resorbable membrane after 5 years follow-up [26]. In addition, it has to be mentioned that in all included comparative studies in this review there were no statistically significant differences between the test and control groups in terms of clinical outcomes [13,15-17].

The results reported by one of the studies [16] showed comparable and statistically significant short-term PPD reduction and CAL gain between the PTGs and the XGF define XGF + membrane groups. Despite the changes being higher in the PTGs group, the difference was statistically insignificant. Similar short-term results were reported in a case series using nano-crystalline hydroxyapatite and bovine-derived xenograft in combination with collagen membrane with mean CAL change from 7.5 mm ± 0.8 to 5.7 mm ± 1.0 and from 7.5 mm ± 1.0 to 5.2 mm ± 0.8 for both groups respectively [27]. A recent prospective study reported on using deproteinized bovine-bone mineral (DBBM) with 10% collagen around 71 peri-implant osseous defects. The mean PPD was significantly reduced by 2.92 mm ± 1.73 and BOP reduced from 71.5% ± 34.4 to 18.3% ± 28.6 [25]. These results were comparable to those reported in the multicentre RCT and comparative study using PTGs [15,16].

In a meta-analysis published in 2016, the authors reported a mean radiographic bone gain of 2.41 mm following regenerative therapy of peri-implant osseous defects using different regenerative materials in a healing period of > 3 years [23], which is almost the same figure reported by other systematic reviews [5,21].

With regard to the amount of bone gain using PTGs, the included studies illustrated significant increase in the defect bone fill and were statistically significant compared with OFD alone. The radiographic defect fill in the included studies was similar and in some occasions more than that reported in other studies using different bone grafting materials and substitutes [5,21,47]. Mean defect infill was also reported as: 57% [13], > 2 mm bone gain [14], marginal bone gain (mesial/distal) of 79%/74.22% [15] and 1.74 mm ± 0.65 [16].

Despite noting the above-mentioned clinical and radiographic improvements, none of the included studies or previous studies using different regenerative materials and techniques resulted in complete disease resolution, and only 30 to 50% disease resolution was obtained [5,15,21]. In one study [15], the author reported that one defect treated with OFD alone resulted in complete radiographic defect fill 12 months after the procedure.

The aim of this review was to look at the available evidence and report on using PTGs as a reconstructive approach for treating peri-implant osseous defects. According to the data collected from the included papers, using PTGs can be a viable option for treating such defects.

LIMITATIONS

Even if a comprehensive and complete investigation and analysis of the effect of the surgical treatment of peri-implantitis has been performed, there are some limitations to this review. First of all, only a few studies were available (7 studies in 10 published papers), only two of which were RCTs and again with few number of patients and implants included. Secondly, every study has a different design moving from animal experiments to RCT in the hierarchy of evidence, which make statistical analysis impossible to achieve. Finally, given that the peri-implantitis field of research is relatively new, it is not surprising that there are different surgical and non-surgical treatment approaches reported in the literature. Until now, there is no specific treatment protocol shown to be significantly more effective (i.e. a gold standard) than the other, so no treatment can be considered as a control in an RCT [21].

CONCLUSION

The authors concluded that using PTGs for the surgical management of peri-implant osseous defects could be more appropriate than using XGF, due to their inert structure and their ability to provide mechanical support for increasing the implant surface area. More clinical studies are needed, with a longer follow-up to allow a better understanding of the benefits of PGT as a regenerative material for peri-implant defects.

REFERENCES

1. Mishra SK, Chowdhary R, Chrcanovic BR, Brånemark PI. Osseoperception in dental implants: A systematic review. J Prosthodont. 2016; 25(3):185-95.

2. Monje A, Aranda L, Diaz KT, Alarcón MA, Bagramian RA, Wang HL, et al. Impact of maintenance therapy for the prevention of peri-implant diseases: a systematic review and meta-analysis. J Dent Res. 2016; 95(4): 372-9.

3. Berglundh T, Armitage G, Araujo MG, Avila‐Ortiz G, Blanco J, Camargo PM, et al. Peri‐implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri‐Implant Diseases and Conditions. J Periodontol. 2018; 89: S313-8.

4. Renvert S, Quirynen M. Risk indicators for peri‐implantitis. A narrative review. Clin Oral Implants Res. 2015; 26: 15-44.

5. Daugela P, Cicciù M, Saulacic N. Surgical regenerative treatments for peri-implantitis: Meta-analysis of recent findings in a systematic literature review. J Oral Maxillofac Res. 2016; 7(3).

6. Chan HL, Lin GH, Suarez F, MacEachern M, Wang HL. Surgical management of peri‐implantitis: A systematic review and meta‐analysis of treatment outcomes. J Periodontol. 2014; 85(8): 1027-41.

7. Alffram PA, Bruce L, Bjursten LM, Andersson GB, Urban RM. Implantation of the femoral stem into a bed of titanium granules using vibration. Upsala J Med Sci. 2007; 112(2): 183-9.

8. Turner TM, Urban RM, Hall DJ, Andersson GB. Bone in growth through porous titanium granulate around a femoral stem. Upsala J Med Sci. 2007; 112(2): 191-7.

9. Wohlfahrt JC, Monjo M, Rønold HJ, Aass AM, Ellingsen JE, Lyngstadaas SP. Porous titanium granules promote bone healing and growth in rabbit tibia peri‐implant osseous defects. Clin Oral Implants Res. 2010; 21(2): 165-73.

10. Lee JS, Sohn JY, Lim HC, Jung UW, Choi SH. Different bone regeneration patterns in periimplant circumferential gap defects grafted with two types of osteoconductive biomaterial. J Biomed Mater Res. Part B: Applied Biomaterials. 2016; 104(6): 1202-9.

11. Thor A. Porous titanium granules and blood for bone regeneration around dental implants: Report of four cases and review of the literature. Case Reports Dent. 2013.

12. Wohlfahrt JC, Aass AM, Rønold HJ, Lyngstadaas SP. Micro CT and human histological analysis of a peri-implant osseous defect grafted with porous titanium granules: a case report. Int J Oral Max Impl. 2011; 26(1).

13. Wohlfahrt JC, Lyngstadaas SP, Rønold HJ, Saxegaard E, Ellingsen JE, Karlsson S, et al. Porous titanium granules in the surgical treatment of peri-implant osseous defects: a randomized clinical trial. Int J Oral Max Impl. 2012; 27(2).

14. Mijiritsky E, Yatzkaier G, Mazor Z, Lorean A, Levin L. The use of porous titanium granules for treatment of peri-implantitis lesions: preliminary clinical and radiographic results in humans. Br Dent J. 2013; 214(5): E13.

15. Jepsen K, et al., Reconstruction of Peri-implant Osseous Defects: A Multicenter Randomized Trial. J Dent Res. 2016; 95(1): 58-66.

16. Guler B, Uraz A, Yalım M, Bozkaya S. The comparison of porous titanium granule and xenograft in the surgical treatment of peri‐implantitis: A prospective clinical study. Clin Implant Dent Res. 2017; 19(2): 316-27.

17. Andersen H, Aass AM, Wohlfahrt JC. Porous titanium granules in the treatment of peri-implant osseous defects—a 7-year follow-up study. Int. J. Implant Dent. 2017; 3(1): 50.

18. Zitzmann, NU, T. Berglundh. Definition and prevalence of peri-implant diseases. J Clin Periodontol. 2008; 35(8 Suppl): 286-91.

19. Renvert S, Polyzois I, Maguire R. Re‐osseointegration on previously contaminated surfaces: a systematic review. Clin Oral Implants Res. 2009; 20: 216-27.

20. Claffey, N, et al. Surgical treatment of peri-implantitis. J Clin Periodontol. 2008; 35(8 Suppl): 316-32.

21. Heitz-Mayfield LJ, Mombelli A. The therapy of peri-implantitis: a systematic review. International Int J Oral Max Impl. 2014; 29.

22. Khoshkam V, Chan HL, Lin GH, MacEachern MP, Monje A, Suarez F, et al. Reconstructive procedures for treating peri-implantitis: a systematic review. J Dent Res. 2013; 92(12 suppl): 131S-8S.

23. Khoshkam V, Del Amo FS, Monje A, Lin GH, Chan HL, Wang HL. Long-term Radiographic and Clinical Outcomes of Regenerative Approach for Treating Peri-implantitis: A Systematic Review and Meta-analysis. Int J Oral Max Impl. 2016; 31(6).

24. Leonhardt Å, Dahlén G, Renvert S. Five‐year clinical, microbiological, and radiological outcome following treatment of peri‐implantitis in man. J Periodontol. 2003; 74(10): 1415-22.

25. Roccuzzo M, Gaudioso L, Lungo M, Dalmasso P. Surgical therapy of single peri‐implantitis intrabony defects, by means of deproteinized bovine bone mineral with 10% collagen. J Clin Periodontol. 2016; 43(3): 311-8.

26. Roos-Jansaker, A.M., et al., Surgical treatment of peri-implantitis using a bone substitute with or without a resorbable membrane: a 5-year follow-up. J Clin Periodontol, 2014; 41(11): 1108-14.

27. Schwarz F, Bieling K, Latz T, Nuesry E, Becker J. Healing of intrabony peri‐implantitis defects following application of a nanocrystalline hydroxyapatite (Ostim™) or a bovine‐derived xenograft (Bio‐Oss™) in combination with a collagen membrane (Bio‐Gide™). A case series. J Clin Periodontol. 2006; 33(7): 491-9.

28. Schwarz F, John G, Schmucker A, Sahm N, Becker J. Combined surgical therapy of advanced peri‐implantitis evaluating two methods of surface decontamination: A 7‐year follow‐up observation. J Clin Periodontol. 2017; 44(3): 337-42.

29. Serino G, Turri A. Outcome of surgical treatment of peri‐implantitis: results from a 2‐year prospective clinical study in humans. Clin Oral Implants Res. 2011; 22(11): 1214-20.

30. Silvestri, M, G Rasperini, S Milani. 120 infrabony defects treated with regenerative therapy: long-term results. J Periodontol . 2011; 82(5): 668-75.

31. Grunder U, Hürzeler MB, Schüpbach P, Strub JR. Treatment of ligature-induced peri-implantitis using guided tissue regeneration: a clinical and histologic study in the beagle dog. Int J Oral Max Impl. 1993; 8: 282.

32. Hurzeler, MB, et al. Treatment of peri-implantitis using guided bone regeneration and bone grafts, alone or in combination, in beagle dogs. Part 2: Histologic findings. Int J Oral Maxillofac Implants. 1997; 12(2): 168-75.

33. Jovanovic SA, Kenney EB, Carranza Jr FA, Donath K. The regenerative potential of plaque-induced peri-implant bone defects treated by a submerged membrane technique: an experimental study. Int J Oral Maxillofac Implants. 1993; 8(1).

34. Nociti, FH, et al., Absorbable versus nonabsorbable membranes and bone grafts in the treatment of ligature-induced peri-implantitis defects in dogs: a histometric investigation. Int J Oral Maxillofac Implants, 2001; 16(5): 646-52.

35. Nociti Jr FH, Machado MÂ, Stefani CM, Sallum EA, Sallum AW. Absorbable versus nonabsorbable membranes and bone grafts in the treatment of ligature‐induced peri‐implantitis defects in dogs: Part I. A clinical investigation. Clin Oral Implants Res. 2001; 12(2): 115-20.

36. Persson LG, Berglundh T, Lindhe J, Sennerby L. Re‐osseointegration after treatment of peri‐implantitis at different implant surfaces: An experimental study in the dog. Clin Oral Implants Res. 2001; 12(6): 595-603.

37. Schou S, Holmstrup P, Jørgensen T, Skovgaard LT, Stoltze K, Hjørting‐Hansen E, et al. Anorganic porous bovine‐derived bone mineral (Bio‐Oss®) and ePTFE membrane in the treatment of peri‐implantitis in cynomolgus monkeys. Clin Oral Implants Res. 2003; 14(5): 535-47.

38. Schou S, Holmstrup P, Jørgensen T, Skovgaard LT, Stoltze K, Hjørting‐Hansen E, et al. Implant surface preparation in the surgical treatment of experimental peri‐implantitis with autogenous bone graft and ePTFE membrane in cynomolgus monkeys. Clin Oral Implants Res. 2003; 14(4): 412-22.

39. Schou S, Holmstrup P, Jørgensen T, Stoltze K, Hjørting‐Hansen E, Wenzel A. Autogenous bone graft and ePTFE membrane in the treatment of peri‐implantitis. I. Clinical and radiographic observations in cynomolgus monkeys. Clin Oral Implants Res. 2003; 14(4): 391-403.

40. Schou S, et al. Autogenous bone graft and ePTFE membrane in the treatment of peri-implantitis. II. Stereologic and histologic observations in cynomolgus monkeys. Clin Oral Implants Res. 2003; 14(4): 404-11.

41. Burchardt H. The biology of bone graft repair. Clin Orthopaedics Related Res. 1983; 4(174): 28-42.

42. Hämmerle CH, Chiantella GC, Karring T, Lang NP. The effect of a deproteinized bovine bone mineral on bone regeneration around titanium dental implants®. Clin Oral Implants Res. 1998; 9(3): 151-62.

43. Hämmerle CH, Karring T. Guided bone regeneration at oral implant sites. Periodontol. 1998; 17(1): 151-75.

44. Heneghan C, B Goldacre, K.R. Mahtani. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017; 18(1): 122.

45. Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. Bmj. 2011; 343: d7995.

46. Faggion Jr CM, Listl S, Tu YK. Assessment of endpoints in studies on peri-implantitis treatment—a systematic review. J Dent. 2010; 38(6): 443-50.

47. Steven-Howe M, Richards D. Surgical regenerative treatment of peri-implantitis. Evid-Based Dent. 2017; 18(3): 79-81.

48. Wohlfahrt JC, Aass AM, Granfeldt F, Lyngstadaas SP, Reseland JE. Sulcus fluid bone marker levels and the outcome of surgical treatment of peri‐implantitis. J Clin Periodontol. 2014; 41(4): 424-31.