2026

Regeneration of the implant-bone connection: a systematic literature review

BOSTON UNIVERSITY

HENRY M. GOLDMAN SCHOOL OF DENTAL MEDICINE

THESIS

REGENERATION OF THE IMPLANT-BONE CONNECTION: A SYSTEMATIC LITERATURE REVIEW

by

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DDS, Mahidol University, 2018

Submitted in partial fulfillment of the requirements for the degree of

Masters of Science in Dentistry

In the Department of Periodontology

2025

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REGENERATION OF THE IMPLANT-BONE CONNECTION: A SYSTEMATIC LITERATURE REVIEW

PEERAPOL TEVAVICHULADA

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ABSTRACT

This systematic literature review investigates the potential for regenerating the bone-to-implant connection (osseointegration) in cases of peri-implantitis by evaluating histological evidence from animal and human studies. A total of 27 studies, including 24 animal and 3 human case reports, were analyzed to assess bone-to-implant contact (BIC) and bone gain following regenerative treatments. The results indicate that while complete re-osseointegration is rarely achieved, partial re-osseointegration has been histologically observed on roughened implant surfaces. Factors influencing outcomes include original implant surface characteristics, defect morphology, decontamination protocols, graft materials, and the use of biologics such as recombinant human bone morphogenetic protein-2 (rhBMP-2). In these studies, re-osseointegration may occur in the apical region of peri-implant defects, while the coronal area is often occupied by soft tissue or mineralized tissue that does not make direct contact with the implant surface. The current evidence is insufficient to draw definitive comparisons between various decontamination techniques, regenerative approaches, or grafting materials.

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GLOSSARY

Term	Definition
Bone-to-implant contact (BIC)	A percentage measure of the direct contact between the bone and the surface of a dental implant.
Bone gain	A linear measurement measured from the bottom of the defect to the coronal part of new bone formation.
Fibro-osseointegration	A condition where fibrous connective tissue forms between an implant and the surrounding bone
Osseointegration	Osseointegration is direct contact between an implant and remodeling bone.
Re-osseointegration	The re-establishment of bone-to-implant integration after bone loss.

INTRODUCTION

Osseointegration was originally defined by Brånemark and Albrektsson as a direct contact between an implant and remodeling bone (1981,1983)(1,2). In contrast, Davies showed a noncollagenous "cement line" formed between the implant surface and new bone formation in his In vitro model (1998)(3). In response, Steflik, using a Transmission Electron Microscope to evaluate the bone-implant interface, and described osseointegration as a dynamic process where a collagenous matrix is laid down directly at the implant surface and then mineralized. The mineralized matrix was separated from the implant by only an electron-dense deposit measuring 20 to 50 nm, suggested as a proteoglycan layer (1994,1998)(4,5). An alternate definition recently proposed by Albrektsson, which describes osteointegration as a foreign body reaction in which bone is formed as a defense mechanism to wall off the implant from the surrounding tissues (2023)(6). Rather than being a simple bone healing response, osseointegration can be considered as an osteoimmune reaction. This process would then be regulated by immune responses mainly from macrophages. M1 macrophages are pro-inflammatory and are involved in the initial immune response. M2 macrophages promote tissue repair and control bone formation. This definition, referred to as a Foreign Body Equilibrium, allows for the view that the body continuously regulates the interaction between the implant and surrounding tissues to maintain balance. If inflammation (due to infection, mechanical overload, or immune disturbances) persists, immune osteoclastic activity is triggered, leading to marginal bone loss and possibly implant failure.

Disruption of the implant-bone connection can compromise the longevity of dental implants. According to the consensus report of the World Workshop on the

Classification of Periodontal and Peri-implant Diseases and Conditions (2017), peri-implant states of health can be categorized by clinical observation as peri-implant health, peri-implant mucositis, peri-implantitis, and peri-implant hard and soft tissue deficiencies. Peri-implant mucositis is characterized by bleeding on probing and visual signs of inflammation. Peri-implantitis is a plaque-associated condition that causes inflammation and bone loss around dental implants. Hard and soft tissue implant site deficiencies refer to conditions where there is insufficient hard and soft tissue at the intended site for a dental implant. These deficiencies can compromise the proper placement, stability, and long-term success of dental implants. A systematic review (2015), showed the incidence of peri-implant mucositis and peri-implantitis ranged from 19 to 65% and from 1 to 47%, respectively (7).

Once osseointegration is disrupted, the clinical challenge would be to resolve inflammation and regenerate the implant-bone connection. Many approaches have been proposed including non-surgical and surgical treatments. Non-surgical treatment with oral hygiene reinforcement is a standard of care for peri-implant mucositis. In peri-implantitis cases, non-surgical treatment alone or with adjunctive treatment such as local/systematic antibiotics or laser therapy have demonstrated limited resolution. Surgical treatments have been proposed in peri-implantitis cases; however, no specific treatment has resulted in a predictable and effective regeneration of bone around dental implants.

The purpose of this systematic literature review was to examine the histologic evidence for regeneration of the implant-bone connection in animal and human models.

MATERIALS AND METHODS

The primary research question framed for this systematic review was "What is the evidence for regeneration of a bone-to-implant contacted interface after peri-implantitis treatment?". This question was structured according to the PICO format.

PICO Format

P (Population/Problem): Patients diagnosed with peri-implantitis or animal research with experimental periodontitis undergoing treatment for re-osseointegration. (Specifically, examining the bone-to-implant contacted interface after regeneration attempts in peri-implantitis treatments)

I (Intervention): Regenerative treatment for peri-implantitis.

C (Comparison): No comparison group (None).

O (Outcome): Formation of a new direct bone-to-implant contact on implant surfaces after regenerative treatment with histologic evidence.

A systematic review searched two electronic databases (Embase, PubMed) for articles up to July 31st, 2023. Selected studies were either animal or human model studies treating peri-implantitis. The primary outcome was histologic assessment of re-osseointegration and bone-to-implant contact. The search was completed in August 2023 on PubMed using the search terms; "(Periimplantitis OR peri-implantitis OR peri implantitis OR "Peri-Implantitis"[Mesh]) AND (re osseointegration OR reosseointegration OR re-integration OR reintegration OR regeneration) AND (histomorphometric OR histology OR histometric OR histologic OR "histology" [Mesh]).

Search on Embase database used terms “(Periimplantitis OR peri-implantitis OR peri implantitis) AND (reosseointegration OR re-integration OR reintegration OR regeneration) AND (histomorphometric OR histology OR histometric OR histologic)”

Inclusion and Exclusion criteria were used to narrow the search.

Inclusion criteria

- Language: English language
- In vivo studies (animal and human)
- Human/animal research with histological evidence
- Treatments to achieve re-osseointegration.
- Studies included induced peri-implantitis in animal models
- Regenerative treatment after peri-implantitis

Exclusion criteria

- Studies including pre-created defects before the implant placement
- unrelated, duplicated, unavailable full texts, or abstract-only papers
- Non-surgical treatment or purely resective surgery of peri-implantitis
- Other systematic reviews
- No BIC measures were made

Study selection and characteristic

In the initial stage of literature selection, one independent reviewer (P. T.) screened the titles and abstracts of all identified studies for eligibility based on the established inclusion criteria. In the second stage, full texts of potentially eligible articles were reviewed and assessed according to the specified exclusion criteria.

The review protocol was developed and structured according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) Statement Research strategy.

RESULTS

The PRISMA flowchart shows the selection process (Fig. 1). The search results were 188 studies from PubMed and 127 studies from Embase databases. Duplications were sorted out using EndNote software. Articles were screened (233) following the inclusion and exclusion criteria, resulting in 33 studies for full-text analysis. Six studies were excluded because they did not have re-osseointegration and bone-to-implant contact (BIC) measurements. The final number of studies included in the review was 27. Three studies were case reports in human subjects.

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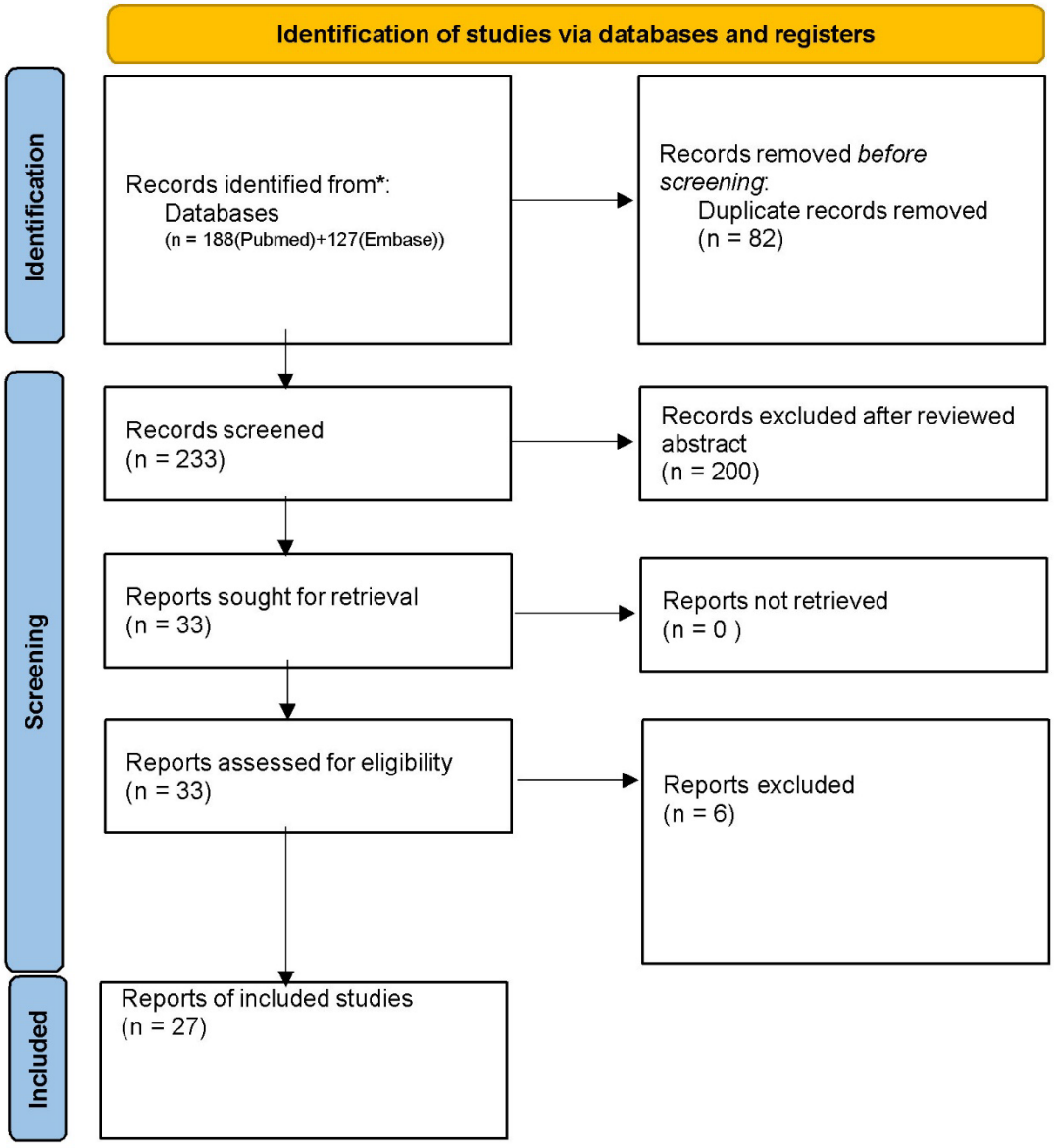

Figure 1 PRISMA flow diagram of studies' screening and selection

The twenty-four animal studies are profiled in Table 1. Included were 18 studies in dogs, 1 study in pigs, and 4 studies in monkeys. All animal studies utilized a ligature model to induce peri-implantitis with varying durations from 4 weeks to 18 months. These articles were then subdivided and analyzed in terms of the intervention used to regenerate peri-implant defects as listed below.

1. Four studies compared the effect of different implant surfaces including sandblasted and acid-etched (SLA), hydroxyapatite-coated (HA), titanium plasma-sprayed (TPS), anodized (A), and machined (M) surfaces. Findings from these studies indicated that roughened surfaces (SLA, HA, and TPS) exhibited superior BIC percentages and bone regeneration compared to machined surfaces (8–11).
2. Six studies compared the effect of different decontamination methods. Decontamination procedures ranged from mechanical debridement, air-powder abrasion, citric acid application, and chlorhexidine irrigation (12–17).
3. Nine studies experimented with different graft materials used to regenerate peri-implant defects (18–26). These materials included Deproteinized bovine bone mineral (DBBM), Biphasic bone graft materials, Demineralized freeze-dried bone (DFDB) and autogenous bone grafts.
4. Five studies investigated the use of the biologic additive rhBMP-2. RhBMP-2 was delivered using various carriers, such as collagen sponges and biomimetic calcium phosphate coatings (27–31).

The primary outcome measured was bone-to-implant contact (BIC) as an indicator of re-osseointegration (defined as new bone formation in direct contact with a previously contaminated implant surface). The secondary outcome measured was vertical bone gain. Bone gain was measured by linear measurement of new bone formation from the defect depth to the restorative platform of the implant. To identify BIC in animal studies, 19 studies used a light microscope (magnification ranged from 1.5x-100x), 1 study used a scanning electron microscope, and 4 studies did not specify the instrument used.

Table 1 Animal study variables

Author/Year	Animal	Implants (n)	Surface[1]	Peri-implantitis induction	Defect configuration	Decontamination procedure	Treatment[2]	BIC (%)[3]	Bone gain (mm)[3]
1. Singh et al. 1993	2 pigs	12	Not described	Ligature 6 weeks	Not described	Air prophylaxis	Group 1: PTFE+submerge Group 2: submerge Control: PTFE+non submerge	Group 1: 35.6 Group 2: 7.8 Control: 0†	Group 1: 2.13 Group 2: 1.37 Control: 0.87†
2. Hürzeler et al. 1995	4 dogs	24	M	Ligature 3 months	Wide and infrabony circumferential	Air-powder abrasive	Group 1: canine DFDB+GTR Group 2: GTR Group 3: HA+GTR Group 4: canine DFDB Gropu 5: HA Control: debridement only	Not described	Group 1: 3.8 ± 0.8 Group 2: 3.6 ± 0.4 Group 3: 3.2 ± 0.6 Group 4: 2.2 ± 0.4 Group 5: 1.8 ± 0.3 Control: 0.5 ± 0.3*
3. Hürzeler et al. 1997	7 dogs	42	M	Ligature 3 months	Wide and infrabony circumferential	Air-powder abrasive	Group 1: HA + GTR (PTFE membrane) Group 2: canine DFDB + GTR (PTFE membrane) Group 3: GTR (PTFE membrane) Group 4: canine DFDB Group 5: HA Control: debridement only	Not described	Group 1: 2.3 ± 0.6 Group 2: 2.2 ± 0.4 Group 3: 1.0 ± 0.2 Group 4: 0.9 ± 0.3 Group 5: 0.9 ± 0.4 Control 0.3 ± 0.3*
4. Hanisch et al. 1997	4 monkeys	32	HA-coated	Ligature 10 months	Not described	Citric acid Air-powder abrasive	Test group: rhBMP-2 in collagen sponge carrier Control group: Collagen carrier	Test group: 29.0 ± 10.5 Control group: 3.5 ± 2.5*	Test group: 2.6 ± 1.2 Control: 0.8 ± 0.8*

1. SLA=Sandblasted and Acid-etched, S=Sandblasted, A= Acid-etched, M=Machined, HA= Hydroxyapatite coated, A= Anodized, T=Titanium plasma sprayed
2. 2. DBBM= Deproteinized bovine bone material, DFDB=Demineralized freeze-dried bone, PTFE= d-Polytetrafluoroethylene, rhBMP-2= recombinant human bone morphogenetic protein-2
3. The method used to evaluate BIC and Bone gain: *light microscope, †scanning electron microscope, §unspecified the used instrument

Table 1 (continued)

Author/Year	Animal	Implants (n)	Surface[1]	Peri-implantitis induction	Defect configuration	Decontamination procedure	Treatment[2]	BIC (%)[3]	Bone gain (mm)[3]
5. Wetzel et al. 1999	7 dogs	41	Group 1: TPS Group 2: SLA Control: M	Ligature 4 months	Not described	Curette Chlorhexidine	Group 1: PTFE membrane Group 2: PTFE membrane Control: debridement only	Group 1: 68 Group 2: 76 Control: 62*	Group 1: 2.6 Group 2: 2.3 Control: 2.2*
6. Machado et al. 2000	5 mongrel dogs	20	A	Ligature 1 month	Not described	Air-powder abrasive	Group 1: GTR (PTFE membrane) Group 2: DBBM Group 3: DBBM+GTR (PTFE membrane) Control: debridement only	Group 1: 30.74% ± 19.71 Group 2: 28.12% ± 23.38 Group 3: 27.18% ± 6.95 Control: 26.86% ± 13.21*	Not described
7. Nociti et al. 2001	5 dogs	15	A	Ligature 4 weeks	Not described	Titanium curette Air-powder abrasive	Group 1: PTFE membrane + DBBM Group 2: collagen membrane + DBBM Group 3: PTFE membrane Group 4: collagen membrane Group 5: DBBM Control: debridement only	Group 1: 27.18 ± 6.95 Group 2: 25.62 ± 16.18 Group 3: 30.75 ± 19.71 Group 4: 26.67 ± 12.89 Group 5: 28.04 ± 23.20 Control: 26.86 ± 13.21*	Not described
8. Schou et al. 2003(1)	8 monkeys	64	TPS	Ligature 9-18 months	4-6 mm bone loss around implants	Chlorhexidine Saline	Group 1: DBBM + PTFE membrane Group 2: DBBM Group 3: PTFE membrane Control: debridement only	Group 1: 36 Group 2,3, control: 15-24§	Group 1: 5.0 Group 2: 4.6 Group 3: 3.7 Control 2.1§

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3. The method used to evaluate BIC and Bone gain: *light microscope, †scanning electron microscope, §unspecified the used instrument

Table 1 (continued)

Author/Year	Animal	Implants (n)	Surface[1]	Peri-implantitis induction	Defect configuration	Decontamination procedure	Treatment[2]	BIC (%)[3]	Bone gain (mm)[3]
9. Schou et al. 2003(2)	8 monkeys	64	TPS	Ligature 9-17 months	4-6 mm bone loss around implants	Group 1: Air-powder abrasive+citric acid Group 2: Air-powder Group 3: Citric acid Control: Chlorhexidine and saline	Autogenous bone+PTFE	39-46% for all groups§	4.4-4.7 mm for all groups§
10. Schou et al. 2003(3)	8 monkeys	64	TPS	Ligature 14-22 months	4-6 mm bone loss around implants	Chlorhexidine and saline.	Group 1: autogenous bone+PTFE membrane Group 2: autogenous bone Group 3: PTFE membrane Control: debridement only	Group 1: 45 Group 2: 22 Group 3: 21 Control: 14*	Group 1: 4.7 Group 2: 4.0 Group 3: 3.0 Control: 1.9*
11. Shibli et al. 2003	6 dogs	36	Group 1: HA-coated Group 2: TPS Group 3: A Control: M	Ligature 2 months and 12 months of natural	Not described	Plastic curet, and saline Toluidine blue O GaAlAs diode laser	PTFE membrane	Group 1 :75.69% ± 12.94 Group 2: 58.95% ± 2.43 Group 3: 62.40% ± 9.62 Control: 52.73% ± 4.47*	Not described
12. Persson et al. 2004	4 dogs	16	1. M 2. SLA	Ligature 3 months	Not described	Test group: CO2 laser therapy +hydrogen peroxide Control: Saline	Only decontamination	M Surface Test group: 59.3 ± 8.4% Control: 67.6 ± 10.3% SLA surface Test group: 72.1 ± 12.4% Control: 62.9 ± 2.1%*	M surface Test group: 0.46 ± 0.14 Control: 0.42 ± 0.13 SLA surface Test group 1.13 ± 0.32 Control: 1.22 ± 0.35*

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Table 1 (continued)

Author/Year	Animal	Implants (n)	Surface[1]	Peri-implantitis induction	Defect configuration	Decontamination procedure	Treatment[2]	BIC (%)[3]	Bone gain (mm)[3]
13. Shibli et al. 2006	5 dogs	40	Group 1: TPS Group 2: S Group 3:A Control: M	Ligature 3 months	Not described	Plastic curet, and saline Toluidine blue O GaAlAs diode laser	PTFE membrane	Group 1: 31.19 ± 17.55 Group 2: 34.69 ± 9.49 Group 3: 41.53 ± 20.28 Control: 41.90 ± 32.71*	Not described
14. Parlar et al. 2009	9 dogs	50	1. M 2. SLA 3. TPS	Ligature 3 months	Not described	Group 1: Change exchangeable intraosseous implant cylinder (EIIC) Group 2: Air-polishing device. Group 3: Cleansing EIIC outside the oral cavity by steam-sterilizing in an autoclave	Resorbable collagen barrier membrane	All groups mean BIC 62.3 ± 18.2%*	Not described
15. Schwarz et al. 2011	6 dogs	48	SLA	Ligature 4 months	Class Ib,Ic,Ie	Plastic curette Saline	Group 1: DBBM+equine bone block+collagen membrane Group 2: DBBM+implantoplasty+collagen membrane Group 3: DBBM+euine bone block+rhBMP-2+collagen membrane Group 4: DBBM+implantoplasty+rhBMP-2+collagen membrane	Group 1: 13.1 ± 12.3 Group 2: 13.7 ± 11.4 Group 3: 21.1 ± 20.0 Group 4: 26.8 ± 28.1*	Group 1: 5.1 ± 1.8 Group 2: 3.9 ± 1.7 Group 3: 4.2 ± 2.5 Group 4: 3.2 ± 2.3*
16. Namgoong et al. 2015	5 dogs	30	Group 1: SLA Group 2: SA and HA-coated Control: M	Ligature 23 weeks	Not described	Chlorhexidine and saline	resorbable collagen membrane	Group 1: 49.8 ± 39% Group 2: 60.9 ± 39% Control: 40.3 ± 44%*	Group 1: 0.5 ± 0.7 Group 2: 0.5 ± 0.6 Control: 0.1 ± 0.2*

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Table 1 (continued)

Author/Year	Animal	Implants (n)	Surface[1]	Peri-implantitis induction	Defect configuration	Decontamination procedure	Treatment[2]	BIC (%)[3]	Bone gain (mm)[3]
17. Park et al. 2015(1)	6 dogs	24	SLA	Ligature 5 months	Not described	Group 1: Water jet Group 2: Water jet + Superfloss Control: Saline	Equine bone mineral+ resorbable collagen membrane	Group 1: 67.23 ± 38.66 Group 2: 57.05 ± 32.87 Control: 55.63 ± 33.57*	Group 1: 0.97 ± 1.23 Group 2: 1.88 ± 1.79 Control: 0.28 ± 0.15*
18. Park et al. 2015(2)	6 dogs	24	SLA	Ligature 4 months	Not described	Water jet Chlorhexidine	Group 1: canine periodontal ligament stem cells (PDLSC) Group 2: BMP2+PDLSC Control: debridement only	Group 1: 59.9 ± 34.59% Group 2: 69.70 ± 11.95% Control: 80.94 ± 28.58%*	Group 1: 18.82 ± 11.32% Group 2: 2.11 +- 0.74 Control 0.48 ± 0.36*
19. Machtei et al. 2016	5 dogs	30	SLA	Ligature 2 months	Circumferential infrabony defect	24% EDTA	Group 1: β-TCP + collagen membrane Group 2: β-TCP + EPC + collagen membrane Control: debridement only	Group 1: 17.65 ± 3.3 Group 2: 5.68 ± 2.91 Control: 7.55 ± 2.24§	Group 1: 3.29 ± 0.69 Group 2: 4.2 ± 0.92 Control: 3.82 ± 0.73§
20. Ramos et al. 2017	8 dogs	64	SLA	Ligature 2 months	Not described	Group 1: Tetracycline HCL Group 2: Tetracycline HCL + GBR Group 3: Photosensitizer Group 4: Photosensitizer + GBR	GBR with DBBM and resorbable collagen membrane	Group 1: 61.9 ± 21.5 Group 2: 61.0 ± 22.4 Group 3: 68.5 ± 22.2 Group 4: 59.2 ± 11.8*	Group 1: 1.0 ± 0.5 Group 2: 1.0 ± 0.6 Group 3: 1.1 ± 0.5 Group 4: 1.2 ± 0.6*

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Table 1 (continued)

Author/Year	Animal	Implants (n)	Surface[1]	Peri-implantitis induction	Defect configuration	Decontamination procedure	Treatment[2]	BIC (%)[3]	Bone gain (mm)[3]
21. Almohandes et al. 2019	6 dogs	28	1. SLA 2. A	Ligature 12 weeks	Circumferential 3 mm deep, 2-3 mm wide	Mechanical debridement with curette Saline	Group 1: DBBM Group 2: Biphasic bone graft material Group 3: DBBM+collagen membrane Control: debridement only	SLA surface Group 1: 46.75 ± 4.35 Group 2: 73.46 ± 10.60 Group 3: 70.87 ± 7.34 Control: 57.41 ± 9.05 A surface Group 1: 45.23 ± 10.13 Group 2: 45.78 ± 11.31 Group 3: 47.27 ± 13.19 Control: 55.28 ± 9.74*	SLA surface Group 1: 1.81 ± 0.56 Group 2: 1.68 ± 0.32 Group 3: 1.00 ± 0.19 Control: 1.21 ± 0.29 A surface Group 1: 1.37 ± 0.41 Group 2: 1.89 ± 0.80 Group 3: 1.38 ± 0.36 Control: 1.05 ± 0.43*
22. Sanz-Esporrin et al. 2019	6 dogs	36	SLA	Ligature 3 months	69.44% supraosseous defect with infrabony component, 47.06 intraosseous defect	Titanium curettes Titanium brush Chlorhexidine 0.2% Saline	Test group: DBBM+rhBMP-2+resorbable natural collagen membrane Control: DBBM+resorbable natural collagen membrane	Test group: 40.91 ± 13.07 Control: 39.56 ± 5.27*	Test group: 1.01+-0.29 Control 0.92+-0.16*
23. Solderer et al. 2021	12 dogs	48	SLA	Ligature 2 months	Not described	Group 1: air polishing + GBR Group 2: mechanical debridement + air polishing Group 3: mechanical debridement + air polishing + GBR Control: mechanical debridement + GBR	Bovine bone mineral+collagen membrane	Not described	Group 1: 1.98 ± 0.9 Group 2: 2.65 ± 2.45 Group 3: 1.73 ± 1.05 Control: 1.21 ± 0.94§
24. Uijlenbroek et al. 2022	6 dogs	36	SLA	Ligature 12 weeks	Not described	Air abrasive with hydroxyapatite	Group 1: no treatment. Group 2: air abrasive surface cleaning by using hydroxyapatite (SC) Group 3: biomimetically prepared CaP (BioCaP) Group 4: rhBMP-2 adsorbed BioCap Group 5: rhBMP-2 internally incorporated BioCap Group 6: rhBMP-2 coating incorporated BioCap	20-40*	Not described

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3. The method used to evaluate BIC and Bone gain: *light microscope, †scanning electron microscope, §unspecified the used instrument

The three human case reports are summarized in Table 2.

Case 1: Fletcher et al. reported a histological record of re-osseointegration on an anodized surface implant in a human (32). The stable implant which had circumferential bone loss and 8 threads exposed was debrided with curette, NaClO and hydrogen peroxide. Regeneration graft was comprised of bovine bone, nanocrystalline calcium sulfate and a porcine membrane. The combination resulted in a radiographic measure of bone gain of 1.8 mm.

Case 2: Kim et al. reported a human case with histology showing direct bone-to-implant contact after regeneration in peri-implantitis sites (33). Histology from a single human subject, 20 months after peri-implantitis regenerative therapy, showed two SLA implants, one with a three-wall 2x2 mm defect and the other with a 3x2 mm circumferential defect. The implants were debrided with ultrasonic scaler, followed by decontamination with a tetracycline hydrochloride solution and then grafted with a particulate biphasic calcium phosphate bone substitute. Re-osseointegration was measured on these implants 20 months after regeneration using histologic analyses. Bone gain of 1.41 mm and 1.90 mm was shown on exposed distal surface of the first molar implant and the mesial surface of the second molar implant, respectively. Complete re-osseointegration of the defects was not achieved.

Case 3: Bosshardt et al. reported four cases of peri-implantitis which were treated in 3 human subjects with electrolytic cleaning, followed by guided bone regeneration (GBR) using xenogenic bone particles covered with a resorbable collagen membrane (34). All implants

developed a dehiscence at 3 weeks after GBR and peri-implantitis recurred in 6 to 13 months, leading to implant failure and removal. BIC and bone gain were measured at 100x magnification with a light microscope. BIC ranged from 5.7% to 39.0% while bone gain ranged from 0.43 to 4.16 mm, respectively.

Table 2 Human case reports

Author/Year	Human subjects (n)	Implants (n)	Surface[1]	Duration before biopsy	Defect configuration	Decontamination procedure	Treatment	BIC (%)[2]	Bone gain (mm)[2]
1. Fletcher et al. 2017	1	1	A	6 months	Not described	Plastic curette, 0.25% NaClO,1.5% H2O2	Nanocrystalline calcium sulfate (CaSO4) (Nanogen, Orthogen)+ Small-particle bovine bone (BB) (Bio-Oss, Geistlich) + Porcine membrane	Not described	1.8◦
2. Kim et al. 2018	1	2	SLA	20 months	#1 three-wall 2x2 mm defect #2 3x2 mm circumferential defect	Ultrasonic scaler with copper alloy tip	Particulate biphasic calcium phosphate bone substitute (Oseon II, Genoss)	Not described	#1 1.41 #2 1.90§
3. Bosshardt et al. 2022	3	4	#1 HA #2 SLA #3 SLA #4 SLA	6-13 months	Not described	Electrolytic cleaning	#1 Bio-Oss® + autogenous bone (50:50)+ Bio-Gide® #2 Bio-Oss® + autogenous bone (50:50) + Bio-Gide® #3 Bio-Oss® + autogenous bone (50:50) + Bio-Gide® #4 Maxgraft® + autogenous bone + A-PRF + Jason® membrane	#1 21.0% #2 36.9% #3 5.7% #4 39.0 %*	#1 1.65 ± 0.8 #2 3.04 ± 1.05 #3 0.43 ± 0.46 #4 4.16 ± 0.95*

1. SLA= Sandblasted and Acid-etched, HA= Hydroxyapatite coated, A= Anodized

2. The method used to evaluate BIC and Bone gain: *light microscope, †scanning electron microscope, §unspecified method/instrument, ◦peri-apical radiograph

DISCUSSION

From a clinical perspective, the primary goal in these studies addressing peri-implantitis was to stop disease progression, indicated by lack of suppuration, minimal or no bleeding on probing, no additional bone loss, and no probing depth more than 5 mm. Although Cone-beam computed tomography is reliable and provides three-dimensional analysis, artifacts around dental implants may limit its accuracy. Evaluation from peri-apical radiographs was more common in human studies. Parameters such as probing depth, clinical attachment level, and bleeding on probing were used to assess the clinical health and stability of peri-implant tissues after peri-implantitis treatment. However, there were limitations to using these clinical parameters to evaluate peri-implant re-osseointegration.

Histologically, the objective of treatment should be to resolve signs of inflammation in the soft tissues and achieve re-osseointegration of the contaminated implant surface. However, the feasibility of histological studies on human tissue was rare (only available in failed implants). Bone defect filling was primarily assessed through radiography and clinical parameters. As a result, animal studies remain the main reference for researching the biology of re-osseointegration. The applicability of these findings to humans is often uncertain due to factors such as defect configuration, accessibility, and implant macro-geometry, which can influence clinical outcomes.

Animal models are widely used to study bone regeneration in peri-implantitis because they offer controlled conditions, faster healing, and detailed histological insights, but biological differences limit their translation to human treatments (35).

Histomorphometry is often used in peri-implantitis studies conducted in animal models. This approach to confirm peri-implant osseointegration involves examining thin cut non-decalcified bone sections under light microscopy. A qualitative analysis identifies and describes various tissues, including mineralized and fibrous connective tissues. The quantitative analysis conducted through histomorphometry evaluates the degree of bone-implant contact. The key parameter used is measurement of the bone-to-implant contact area (BIC).

A ligature model is the most common method to replicate peri-implantitis and its progression in animal studies. Ligatures can be made of silk, cotton, or stainless-steel wire. The ligature is placed around the implant in a submucosal position. It breaks the mucosal seal around the implant and allows subgingival plaque formation. Peri-implantitis is induced with inflammation followed by severe bone destruction (36,37). The ligature is removed after a few months. It has been argued that the ligature model may not fully represent naturally occurring peri-implantitis in human tissue because the ligatures themselves cause trauma to tissue and increase plaque accumulation (38).

Animal models

Dogs are the most common animal model used for the peri-implantitis model. Dogs have naturally occurring periodontitis and peri-implantitis which can be accelerated by ligature and soft diet. Dog alveolar bone is reported to have a moderately similar composition to human bone. Monkeys are well known to have similar oral structures to humans. However, the specific anatomy of a monkey's jawbone limits the size of dental

implants to a reduced-diameter. Difficulty in maintenance and strict restriction of monkey research models reduced their application in dental research. Minipigs have similar macro and microstructure of jawbone compared to humans. Their jawbone allows the usage of normal implant diameter. However, minipig models were not widely used in peri-implantitis experiments, only 1 report was found (39).

Submerged healing

Submerged healing for regenerative therapy has been proposed in order to achieve primary closure and achieve an undisturbed regenerated area in guided bone regeneration studies. It prevents graft contamination and post-operative infection. Submerged healing favors an environment for bone regeneration and reduces the risk of complications. Non-submerged healing and submerged healing were compared in pigs. Histologic improvements were only observed with the submerged healing groups (22)(T1.1). This suggests that submerged healing may be more effective in promoting bone regeneration compared to non-submerged healing.

Decontamination and Debridement

Decontamination of implant surfaces plays an important role in successful bone regeneration. Of the debridement protocols compared, a combination of mechanical and chemical debridement was the most effective. With regard to chemical debridement, using no specific agent was superior to others including normal saline, hydrogen peroxide and citric acid. The question arises whether it is possible to reconstitute the original surface produced in manufacture. After titanium rods are milled into endosteal implant

shape, and cleaned with solvents they go through the process of surface sterilization deionization and further modification to achieve microroughness which can include a varied surface titanium oxide layer. This oxide layer is the crucial factor that allows osseointegration.

Debridement protocols

A variety of chemical and mechanical protocols or combinations have been tested to clean implant surfaces prior to regenerative treatment. Mechanical debridement can be done with curette, air-abrasion, water jet, or a titanium brush. Various chemical solutions such as chlorhexidine, citric acid, hydrogen peroxide, tetracycline hydrochloride, and saline have been used to decontaminate implants. Park et al. compared debridement methods using a water jet and dental floss in beagle dogs (13)(T1.17). After the debridement, the peri-implant defects were regenerated with equine bone mineral and absorbable membrane. Debridement using a water jet and dental floss resulted in more vertical bone fill when compared to saline alone. Solderer et al. reported no difference in bone regeneration between implants debrided with air polishing and curette (15)(T1.23). Experimentation with implant debridement using air abrasion, citric acid, chlorhexidine, and saline followed by autogenous bone and ePTFE membrane revealed no percentage difference in re-osseointegration among four treatment groups (17)(T1.9). Persson et al. treated experimental peri-implantitis with a carbon dioxide laser and hydrogen peroxide on turned and SLA surface implants in beagle dogs (12)(T1.12). They found no difference in re-osseointegration between tested groups and the control group (saline). However, SLA surfaces had superior BIC when compared to turned surfaces (84% versus

22% respectively). Antimicrobial photodynamic therapy or topical tetracycline hydrochloride combined with or without GBR to regenerate peri-implant defects resulted in no difference between groups.

Membrane and/or bone graft materials

In animal studies, ePTFE membrane with or without bone graft materials were the most frequently used graft materials. Although several studies compared different bone graft materials and membranes to regenerate peri-implantitis, there was not enough evidence to determine whether one bone graft material or membrane was superior to the others. Non-resorbable membranes showed higher complication rates compared to resorbable membranes.

Many studies compared the use of different membranes to regenerate peri-implant defects with or without bone graft. A membrane is used in guided tissue/bone regeneration to exclude soft tissue cells and allow cells from bone to enter. In the early 1990s, expanded PTFE (ePTFE) membranes were widely used. Later in the 2000s, resorbable collagen membranes were introduced and used for regenerative therapy. Experimental peri-implantitis in micro pigs were treated with and without ePTFE membrane under submerged healing (22)(T1.1). In ePTFE group, BIC was 35.6% which is higher than the submerged group without ePTFE membrane (7.8%). Combined autogenous bone graft or Bio-Oss with ePTFE membrane resulted in re-osseointegration and BIC (36-45%) (17–19)(T1.8,9,10).

In studies using different bone graft materials, ePTFE and resorbable membranes to regenerate peri-implant defects, debridement alone resulted in similar results as grafting

with or without membranes (20,26)(T1.6,7). Bone grafts used to treat peri-implantitis may be autogenous, allograft, xenograft or alloplast. Hürzeler et al. compared canine demineralized freeze-dried bone and resorbable hydroxyapatite in beagle dogs with or without ePTFE membrane. There was no difference in bone graft materials in re-osseointegration. However, the combination of ePTFE membrane with canine demineralized freeze-dried bone or resorbable hydroxyapatite resulted in a greater amount of re-osseointegration than other groups (24,25)(T1.2,3).

Graft enhancement

Bone morphogenetic protein

RhBMP-2 is a biologic growth factor, known for its role in osteogenesis. It possesses osteoinductive properties, stimulating the differentiation of mesenchymal stem cells into osteoblasts and promoting new bone formation. Studies have evaluated the role of rhBMP-2 alone or combined with grafting materials to regenerate bone around peri-implant defects. As an example, Peri-implant defects regenerated with rhBMP-2 in an absorbable collagen sponge in rhesus monkeys showed superior results with 2.6 mm (40%) bone gain when compared to the control group (debridement alone) which resulted in 0.8 mm (8.9%) bone gain (27)(T1.4). Vertical bone gain in rhBMP-2 groups was significantly greater than in controls. It was suggested that rhBMP-2 has a strong potential to promote bone regeneration and re-ossointegration in peri-implantitis defect.

Guided bone regeneration, studied in beagle dogs, using deproteinized bovine

bone combined with 10% collagen soaked in rhBMP2, however, failed to show a significant difference from control (the same scaffold and membrane were used, but soaked in saline) in re-osseointegration (31)(T1.22).

BMP2 delivered using canine periodontal ligament stem cells (PDLSCs) and hydroxyapatite to regenerate peri-implantitis defects in beagle dogs showed significant 61.02 % bone gain (69.70% BIC) while PDLSC alone and the control groups were 18.82% (59.96% BIC) and 12.26% (80.94% BIC) respectively (29)(T1.18).

Surfaces and contour of defect

Surface characteristics

Several studies investigated surface characteristics and surface roughness as factors for re-osseointegration. The original Brånemark implant was machine-surfaced and "cleaned" by solvents, sterilization and ion-discharge. Machined surfaces have been shown to have inferior regeneration potential when compared to other surfaces. In response to this issue, addition and reduction chemical methods have been used to increase the roughness of implant surface. The surface modification may be additive, reductive, or a combination of both methods. Common additive methods are plasma spraying and anodization. Reductive methods are sandblasting, laser radiation and acid-etching.

Namgoong et al. compared bone regeneration in experimental peri-implantitis defects in beagle dogs with 3 different implant surfaces; sandblast/acid-etched(SA), sandblast/acid-etched coated with hydroxyapatite, and a machined (M) surface. The lost

integration sites were treated with a resorbable membrane. The BIC measured was significantly greater in SA (49.8%) and SA with hydroxyapatite-coated (60.9%) when compared to the machined surface implants (40.3%). Shibli et al. 2003 treated ligature-induced peri-implantitis with photosensitization and GBR using expanded polytetrafluoroethylene membrane (ePTFE) in mongrel dogs (9)(T1.11). These studies also show higher percentage of BIC in HA, titanium plasma sprayed and acid-etched(AE) (75.69%, 58.95%, 62.40% respectively) compared to commercially pure titanium surfaces (cpTi) (52.73%). In a subsequent study by Shibli et al. 2006, however, no difference in BIC was noted between implant surfaces (cpTi 41.90%, TPS 31.19%, sandblasted 34.69%, AE 41.53%) (10)(T1.13). In contrast, an experimented guided tissue regeneration study, described by Wetzel et al, using ePTFE around induced peri-implantitis defects in beagle dogs showed minimal BIC in all 3 surfaces TPS, SLA and M (14%,20%,2% respectively) (11)(T1.5).

Defect configuration

Regardless of regeneration methods, peri-implant defect morphology plays an important role in regenerative therapy. The size, shape, depth, and extent of the defect can greatly impact the success of regeneration for peri-implantitis. Therefore, understanding and assessing the defect morphology is crucial for determining the appropriate treatment and predicting the outcomes. Thirteen out of twenty-four studies included in the present study did not describe the defect morphology prior to treatment. It is another limitation for the comparison of study results and outcomes in this review.

CONCLUSION

Osseointegration is more than a physical contact between bone and implant. It may be a dynamic, ongoing process influenced by the immune system. Understanding it has implications for the potential of re-osseointegration around implants. However, the definition of osseointegration is not yet agreed upon, it is more challenging to define re-osseointegration. In the absence of agreed definitions, study protocols and analytical methods used to evaluate re-osseointegration are inconsistent. With limited evidence from included studies in the present study, re-osseointegration was considered as direct bone-to-implant contact under histological analysis.

While not providing conclusive evidence, the studies included in this review provided an overview of the possibility for re-osseointegration of previously contaminated implants. There is some histological evidence that re-osseointegration can occur after the treatment of ligature-induced peri-implantitis in animal studies. In these studies, re-osseointegration is generally observed in the most apical portion of the peri-implant defect, with the coronal part filled only with soft tissue or mineralized tissue not in contact with the implant. There is limited evidence to compare different decontamination, regenerative methods, and materials.

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