Efficacy of Decontamination Methods for Biofilm Removal from Dental Implant Surfaces and Reosseointegration: An AAP/AO Systematic Review on Peri-implant Diseases and Conditions

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Purpose: To evaluate the nonclinical evidence concerning the efficacy of different decontamination methods in facilitating reosseointegration, eliminating biofilm from implant surfaces, and their potential to induce adverse surface modifications and release of material remnants. ***Materials and Methods:*** Systematic electronic and manual searches were conducted to identify publications involving animal or human block biopsies, ex vivo/in situ studies, and in vitro studies. Mechanical, chemical, and electrolytic methods for implant decontamination were presented in a descriptive analysis. ***Results:*** A total of 121 studies were included, namely 46 involving animal/human biopsies, 39 ex vivo/in situ experiments, and 36 in vitro investigations. No modality demonstrated significant superiority in terms of reosseointegration outcomes. Ex vivo, in situ, and in vitro studies reported that greater biofilm removal from implant surfaces occurred with polyetheretherketone (PEEK) ultrasonic tips, air-powder abrasive (APA), erbium: yttrium-aluminum-garnet (Er:YAG) laser, and electrolytic cleaning. Minimal surface alterations were noted with soaked cotton pellets, APA, specific settings of Er:YAG laser, erbium, chromium: yttrium-scandium-gallium-garnet (Er,Cr:YSGG) laser, electrolytic treatment, and cold atmospheric plasma. Titanium or stainless steel curettes, ultrasonic tips, titanium brushes, and implantoplasty induced significant surface alterations and peak flattening of implant threads. Plastic and carbon curettes as well as PEEK ultrasonic tips and APA left material remnants. ***Conclusions:*** Implant reosseointegration is possible following appropriate surface decontamination. Application of Er:YAG laser, electrolytic cleaning, and APA stand out as the methods that most closely embody the ideal characteristics of an effective decontamination protocol. *Int J Oral Maxillofac Implants 2025;40(suppl):s91–s160. doi: 10.11607/jomi.2025suppl4*

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Peri-implantitis is characterized by inflammation of the peri-implant mucosa and bone loss around dental implants.[1] This disease poses a significant threat to the long-term survival of implants, thereby requiring a comprehensive understanding of its etiology and effective management strategies.[2] The main etiologic factor for peri-implantitis is the complex microbial biofilm that develops on the surface of exposed titanium or titanium alloys.[3] A "gold standard" treatment protocol that fulfills both clinical and microbiologic criteria for effective and predictable management of peri-implantitis has yet to be established.[4]

Although clinical research of peri-implantitis is essential, clinical studies present significant limitations in understanding the efficacy of decontamination treatments. First, the process of implant decontamination represents just one part of a broader surgical procedure. This includes factors such as flap design, grafting approach, membrane selection, defect morphology, and the patient's individual healing capacity. Thus, the clinical outcomes are contingent upon variables beyond the specific cleaning methods employed. Consequently, understanding the isolated impact of decontamination modalities within the complex context of human studies becomes a difficult endeavor.[5] A second limitation lies in the difficulty of obtaining direct tissue samples or biopsies from sites treated for peri-implantitis. This prevents the comprehensive assessment of the effectiveness of decontamination procedures and especially its

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potential to promote reosseointegration. Additionally, the various factors modulating microbial accumulation and disease progression must be considered.

Preclinical animal studies have been utilized to evaluate the biological response following implant surface decontamination, particularly the potential for reestablishing a bone-to-implant contact (BIC) after surface decontamination (reosseointegration) through histologic analysis.[6] However, these studies are not designed to quantify biofilm removal or evaluate the effects of decontamination on surface characteristics. On the other hand, the in vivo, in situ, and in vitro design allows for systematic assessment and analysis of various decontamination methods to effectively eliminate biofilms from titanium surfaces as well as alterations on the implant surface, reducing external factors related to different surface compositions and configurations as well as host healing and immune responses or implant access location.[7,8]

Extensive efforts have been made to evaluate the clinical outcomes of various decontamination methods in humans, often comparing two techniques.[5] However, previous studies have largely overlooked the broader biological and mechanistic context. To date, no review has comprehensively addressed this topic by integrating the full spectrum of evidence, from the potential for reosseointegration shown in animal and human histologic studies to the surface-level effects of decontamination observed in ex vivo, in situ, and in vitro models. This multidimensional approach is what sets the present review apart. Therefore, the aim of this systematic review was to first assess the evidence regarding the effectiveness of various approaches in promoting reosseointegration post-decontamination based on animal models and human histology. Secondly, the review investigated the efficacy of different decontamination methods employed to remove biofilm from titanium or titanium-alloy surfaces along with its potential to produce surface alterations.

MATERIALS AND METHODS

Protocol and Registration

The present systematic review was developed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[9] The protocol was registered in PROSPERO (CRD42024479946) prior to commencement of the study.

PICO (Population, Intervention, Comparison, and Outcome) Questions

Four different study designs aiming to explore the efficacy of different decontamination methods for removal of biofilm from titanium surfaces and reosseointegration were evaluated:

A. *In vivo:* Animal studies and human case studies in which a block biopsy was obtained after surgical treatment of peri-implantitis
B. *Ex vivo:* Studies in which implants with peri-implantitis were either *(a)* treated intraorally, then explanted and evaluated in the laboratory; or *(b)* explanted and subsequently decontaminated and evaluated in the laboratory
C. *In situ:* Studies with implants or titanium discs that were held within the oral cavity using stents for biofilm accumulation during specific time periods, then decontaminated and evaluated in the laboratory
D. *In vitro:* Studies with implants or titanium discs contaminated in the laboratory, utilizing saliva or an oral bacterial consortium to induce biofilm formation, then decontaminated and evaluated

Ex vivo (b) and in situ (c) studies were combined due to their similarities (oral biofilm formation). Thereafter, the review aimed to answer the following PICO questions[10]:

- **Question 1:** "In animals or humans treated for peri-implantitis from whom implants were removed via block biopsy (a) *(population)*, what is the efficacy of mechanical, chemical, and electrolytic decontamination protocols *(intervention)* in comparison to other intrasurgical implant decontamination methods, including placebo *(comparison)*, concerning the establishment of histologic reosseointegration *(outcomes)*?"
- **Question 2:** "In implants explanted due to peri-implantitis (b) or dental implants/titanium discs exposed to the oral cavity (c) *(population)*, what is the efficacy of mechanical, chemical, and electrolytic decontamination protocols *(intervention)* compared with any other protocols aiming at implant decontamination, including placebo *(comparison)*, in the reduction of bacterial loads/deposits, cleaning efficacy, and alterations in the integrity of the implant surface *(outcomes)*?"
- **Question 3:** "In implants or discs contaminated in a laboratory setting with human biofilm, saliva, or a multispecies bacterial biofilm (d) *(population)*, what is the efficacy of mechanical, chemical, and electrolytic decontamination protocols *(intervention)* compared with any other protocols for surface decontamination, including placebo or sterile uncontaminated samples *(comparison)*, in the reduction of bacterial loads/deposits, cleaning efficacy, and alterations in the integrity of the implant surface *(outcomes)*?"

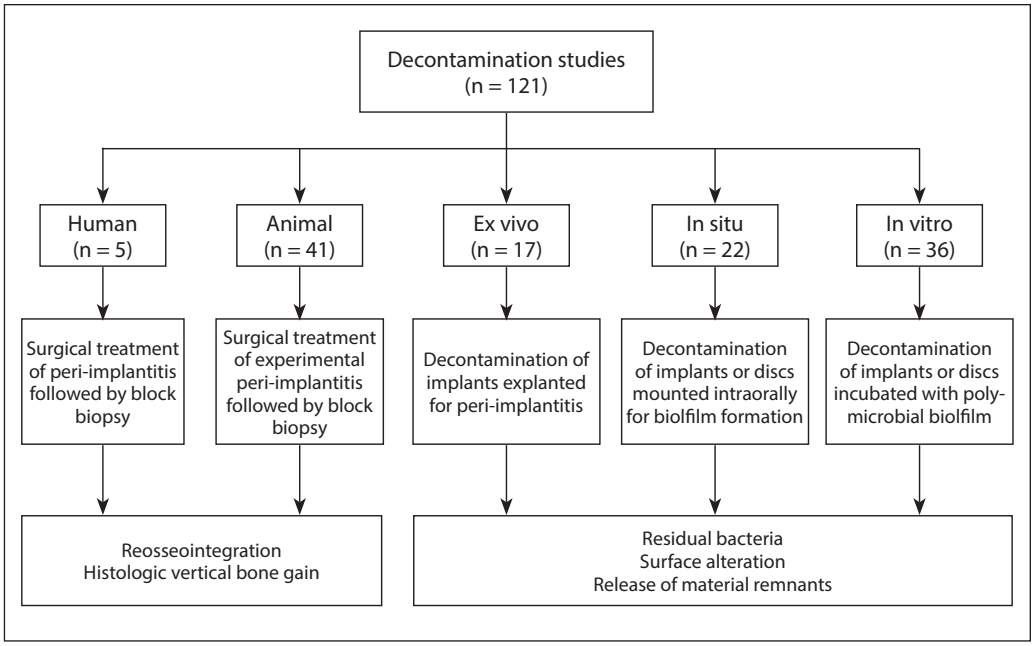

Fig 1 Flowchart summarizing the population and outcomes of interest for each type of study.

A comprehensive systematic search aiming to answer the three PICO questions was conducted on MEDLINE, Embase, Cochrane Central, Web of Science, and Scopus. Titles and abstracts were independently screened by two calibrated reviewers (A.R., M.B.). Inclusion and exclusion criteria as well as information regarding sources and search strategy, selection process, data extraction, risk of bias, and data synthesis are available in the Appendix found at the end of this article.

RESULTS

Study Selection for Each PICO Question

Details regarding study selection are available in the Appendix. A total of 121 publications were included in the present review (Fig 1 and Appendix Fig 1 available at the end of this article): 41 animal experiments and 5 human block biopsy studies,[11–58] 17 ex vivo and 22 in situ experiments,[59–97] and 36 in vitro experiments.[7,98–132]

In Vivo Studies

This section pertains to studies conducted in animals or humans in which a block biopsy was obtained after surgical treatment of peri-implantitis and aimed at exploring the following questions regarding the treatment of experimental peri-implantitis. Results of the literature review are displayed in Appendix Table 1 (see at the end of this article) and are briefly described below.

1. Are systemic antibiotics administered without mechanical decontamination therapy effective in eliminating the peri-implantitis lesion?

The canine study conducted by Ericsson et al[14] in 1996 clearly demonstrated that the use of systemic antibiotics (amoxicillin and metronidazole) without the inclusion of mechanical therapy was ineffective in eliminating peri-implantitis lesions. This was attributed to the persistent inflammatory infiltrate associated with the presence of plaque. In 25% of the examined sites, this infiltrate was found to be in direct contact with the adjacent bone tissue. Therefore, the study emphasized the crucial role of mechanical therapy and implant decontamination in resolving peri-implantitis lesions.

2. Is implant reosseointegration (BIC) possible after the treatment of peri-implantitis?

Implant reosseointegration is defined as the reestablishment of direct BIC to an implant surface after being disrupted. Most studies included in this review evaluated reosseointegration by measuring the percentage of BIC from the base of the bone defect to the most coronal BIC[15,23–27,29,30,37–39,45–47,55,58] (Fig 2). Some studies, however, have assessed the percentage of BIC from the base of the bone defect to the implant shoulder[15,28,31,35,44,46,49] (see Fig 2). Few studies focused on specific areas of the implant, such as 5 mm from the implant shoulder or the three most coronal threads.[13,17,21,32,42,43]

Numerous animal studies have reported reosseointegration after implant decontamination.[11–13,15–18,20–22,24–32,35,37–47,49,52] Within studies that assessed reosseointegration as the percentage of BIC from the

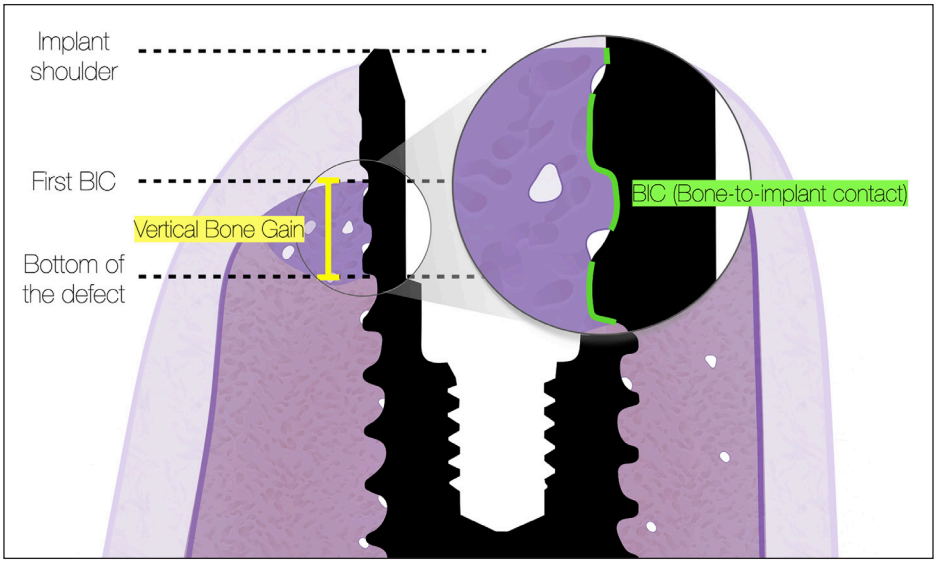

Fig 2 Schematic illustration of the histologic vertical bone gain, determined as the distance between the first bone-to-implant contact and the bottom of the defect, and its corresponding bone-to-implant contact (percentage of reosseointegration). It is important to note that the assessment of reosseointegration from the implant shoulder to the bottom of the defect may potentially result in lower values. This does not necessarily indicate inferior results but rather reflects measurement discrepancies.

base of the bone defect to the most coronal BIC, values ranged from 9% to 85%.[15,24–27,29,30,37–39,45–47] However, contrasting outcomes have also been observed, with some authors reporting either no or inconsistent reosseointegration, characterized by the presence of a soft tissue interface between the bone and the implant surface in specific locations across the specimens despite diligent mechanical decontamination efforts.[14,19,23,28,30,31] Overall, these findings suggest that a previously contaminated implant surface possesses the potential for reosseointegration following appropriate decontamination.

Human biopsy studies are scarce, but reosseointegration has also been demonstrated.[54–58] Wohlfahrt et al used titanium curettes and 24% ethylenediaminetetraacetic acid (EDTA) gel for implant decontamination, followed by grafting with porous titanium granules and submerged healing. After 12 months, a block biopsy showed areas of reosseointegration.[54] Fletcher et al employed mechanical and chemical decontamination by using a plastic curette and sodium hypochlorite, hydrogen peroxide, and sterile saline. Calcium sulfate and bovine bone were used to graft the defects. Reosseointegration was reported in the top three threads coronal to the native bone, resulting in 1.8 mm of vertical bone gain and 37.5% BIC.[55] Kim et al treated two adjacent implants with an ultrasonic scaler and tetracycline hydrochloride solution. Sites were grafted with biphasic calcium phosphate. A block biopsy retrieved after 20 months showed successful reosseointegration, with 1.9 and 1.4 mm of vertical bone gain around the implants.[56] Nevins et al evaluated biopsy samples obtained from three patients who underwent erbium, chromium: yttrium-scandium-gallium-garnet laser (Er,Cr:YSGG) surface decontamination. Sites were grafted with allograft combined with a growth factor and covered by a collagen membrane. Successful reestablishment of BIC on previously contaminated implants was observed 6 months later.[57] Bosshardt et al evaluated four dental implants decontaminated with electrolytic cleaning and treated with xenograft/allograft plus a collagen membrane. The histomorphometric analysis revealed 6% to 39% BIC and 1.3 to 5.2 mm of vertical bone gain.[58] Therefore, similar to animal studies, human biopsy studies suggest that reosseointegration is possible following appropriate surface decontamination.

3. Which mechanical decontamination methods have demonstrated reosseointegration in animal or human studies?

Various mechanical decontamination methods have shown potential for achieving reosseointegration, as indicated by BIC. However, evaluating BIC alone provides limited information into the success of decontamination procedures. It is also important to assess the vertical bone gain—that is, the distance from the base of the bone defect to the most coronal BIC (see Fig 2). For example, 85% BIC with only a 0.5-mm vertical bone gain may be less clinically relevant than 60% BIC with a 2-mm vertical bone gain. Therefore, in this section, reosseointegration outcomes were reviewed in conjunction with the vertical bone gain to provide a more comprehensive assessment. Mechanical methods were described both independently and in combination with other treatments; however, only outcomes from independent applications were considered when drawing conclusions.

Soaked cotton pellets or gauzes

Independent: Four animal studies evaluated reosseointegration outcomes using cotton pellets or gauzes soaked in saline for implant surface decontamination.[19,23,24,29] Two of these studies demonstrated successful reosseointegration (63% BIC) and 1.2-mm vertical bone gain in implants with a macroroughened surface. The same investigations, however, reported poorer outcomes for machined implants, with only 0.4 mm of bone gain (68% BIC).[24,29] The other two studies were performed on implants with an anodized surface and reported minimal vertical bone gain (0.4 mm and 0.3 mm, respectively) and minimal BIC, which was considered a failure of reosseointegration.[19,23]

Curettes

Independent: Two animal studies evaluated the use of curettes alone for implant decontamination—one using plastic[31] and the other using carbon curettes.[52] The first study reported 8.4% BIC from the bone defect to the implant shoulder, but the vertical bone gain was not documented.[31] In the second study, in addition to carbon curettes, xenograft and a membrane were employed. This study reported 1.2 mm of bone gain between the bottom of the bone defect to the first BIC, but the percentage of BIC was not provided.[52]

Combined: Additionally, eight studies described the use of different curettes (stainless steel, titanium, plastic, carbon) in combination with saline-soaked cotton pellets,[35,47] air-powder abrasive (APA),[52] a diode laser,[31,46] chlorhexidine (CHX),[20] topical metronidazole,[30] tetracycline-soaked cotton pellets,[46] or titanium brushes plus CHX[49] for implant surface decontamination. These combinations were used either alone or in association with bone grafts and/or membranes. Reosseointegration outcomes varied, with vertical bone gain ranging from 0.1 to 2.6 mm and BIC ranging from 15% to 73%. One human case study combined plastic curettes with two chemical agents and reported 37.5% BIC and 1.8 mm of vertical bone gain.[55]

Ultrasonic tips

Independent: Reosseointegration outcomes following the use of an ultrasonic scaler for implant decontamination was presented in one animal publication reporting 8.7% BIC and 0.5 mm of vertical bone gain.[30]

Combined: One animal study reported the use of an ultrasonic scaler in combination with CHX and demonstrated minimal vertical bone gain (0.2 mm).[41] A human case study employed a copper-alloy ultrasonic tip and tetracycline hydrochloride solution for surface decontamination around two adjacent implants and reported vertical bone gains of 1.9 and 1.4 mm; a bone graft was also used in conjunction with the decontamination protocol.[56]

PEEK

No animal or human biopsy study investigated the effect of polyetheretherketone (PEEK) ultrasonic tips on reosseointegration.

Titanium brushes

Independent: No animal study reported reosseointegration outcomes when titanium brushes were used alone for the decontamination of infected implants.

Combined: Two studies used titanium brushes in combination with other approaches.[41,49] Carral et al combined titanium brushes with either NaOCl + CHX or CHX alone and reported that reosseointegration was achieved, albeit with minimal vertical bone gain (0.2 mm).[41] Sanz-Esporrin et al applied titanium brushes together with titanium curettes and CHX, as well as bone graft and collagen membrane, and reported 39% to 41% BIC and 0.9 to 1.01 mm of vertical bone gain.[49]

Air-powder abrasive

Independent: APA was the most-studied approach in animal models, with a total of eight studies exploring its efficacy in cleaning contaminated implants as the sole tool.[11,13,16,17,21,22,25,52] Reosseointegration was achieved in all studies, however with varying degrees. One study reported that reosseointegration was achieved with minimal bone gain (ranging from –0.1 to 0.3 mm).[11] Another study observed vertical bone gain ranging from 0.3 to 2.3 mm, depending on whether bone grafts and/or membranes were used.[16] Similarly, reosseointegration was achieved with a vertical bone gain of 1.2 mm when an expanded polytetrafluoroethylene (ePTFE) membrane was applied, compared to 0.6 mm without it.[22] A recent study also noted successful reosseointegration with a 2.6-mm vertical bone gain when both bone graft and membrane were utilized.[52] Four additional investigations reported that reosseointegration was achieved but did not report the vertical bone gain.[13,17,21,25]

Combined: In combination with other biomaterials, three studies used APA and citric acid, reporting BIC ranging from 9% to 46% and vertical bone gain from 0.8 to 2.6 mm.[12,15,25] Another study combined APA with carbon curettes, achieving reosseointegration with 2 mm of vertical bone gain when bone graft and membrane were applied, and 1.7 mm without them.[52] Additionally, a study using APA with a carbon dioxide (CO_2) laser reported reosseointegration, with vertical bone gain of 2.2 mm with an ePTFE membrane and 0.7 mm without it.[22]

Laser therapy

Independent: Laser technologies were explored independently in four animal studies and one human case study encompassing application of four different types

of lasers, namely diode,[28,42] CO_2,[22] erbium: yttrium-aluminum-garnet (Er:YAG)[30,42] and Er,Cr:YSGG.[57] One animal investigation using a CO_2 laser observed reosseointegration with a vertical bone gain of 1.2 mm when an ePTFE membrane was applied and 0.6 mm when it was not.[22] Another study utilizing Er:YAG laser reported successful reosseointegration with a BIC of 44.8% and a vertical bone gain of 1.3 mm.[30] Two animal studies[28,42] and one human case study[57] reported reosseointegration but did not provide details on vertical bone gain.

Combined: In the remaining four animal studies, lasers were used in conjunction with a plastic curette, hydrogen peroxide, and physiologic saline and consistently achieved reosseointegration. A study using a CO_2 laser in conjunction with hydrogen peroxide (H_2O_2) demonstrated successful reosseointegration, with a BIC of 72.1% and a vertical bone gain of 1.1 mm in implants with a macroroughened surface. However, the outcomes were less favorable for turned implants, showing a BIC of 59.3% and a bone gain of only 0.5 mm.[29] When a diode laser was used with plastic curettes, combined or not with bone graft and membranes, reosseointegration was consistently achieved, with BIC values of 61% and 59.2%, respectively, and vertical bone gains of 1.0 and 1.2 mm.[46] Two other studies reported that reosseointegration was achieved after the use of a diode laser but did not provide data on vertical bone gain.[28,31]

Implantoplasty

No animal or human biopsy studies have evaluated the efficacy of implantoplasty, which involves the use of burs to completely smooth the implant surface and threads, as a mechanical decontamination method for reosseointegration. Schwarz et al performed implantoplasty exclusively on the supracrestal component of the defect, so reosseointegration was not assessed in this area.[35] In the study by Htet et al, titanium burs were used to decontaminate the implant surface while preserving the implant threads, which does not constitute implantoplasty. The authors also reported that a 1-mm titanium round bur failed to reach the area between the threads, resulting in a modest 8% BIC.[42]

Electrolytic cleaning

One study in humans evaluated four dental implants treated with electrolytic cleaning as the sole method of decontamination, combined with bone graft and membrane. The study reported successful reosseointegration with BIC values ranging from 5.7% to 39% and vertical bone gains from 1.3 to 5.2 mm.[58]

4. Has any decontamination method shown superior histologic vertical bone gain (mm) in animal or human studies?

Vertical bone gain is defined as the distance from the base of the bone defect to the most coronal BIC. Due to heterogeneity in methodology and therapies among the different studies, it would be methodologically inappropriate to conduct a meta-analysis to determine the most effective method for implant decontamination. Nevertheless, it was feasible to deduct certain insights by qualitatively assessing results from studies that employed the same biomaterials and techniques but differed in decontamination tools.

Titanium brushes versus ultrasonic devices

Carral et al found no statistically significant differences in reosseointegration between using CHX with titanium brushes (0.6 ± 0.3 mm) or with an ultrasonic device with a plastic tip (0.6 ± 0.2 mm).[41]

APA vs plastic curettes

Solderer et al observed no statistically significant difference in vertical bone gain when comparing the use of APA (2.6 ± 2.4 mm), plastic curette (1.2 ± 0.9 mm), or the combination of both (1.9 ± 0.9 mm) in conjunction with bone graft and membranes.[52]

APA vs laser

One study reported similar vertical bone gain when three decontamination methods—APA (0.6 ± 0.7 mm), CO_2 laser (0.6 ± 0.6 mm), or the combination of both (0.7 ± 0.5 mm)—were compared alone. The same study observed increased bone gain when decontamination was followed by the application of an ePTFE membrane, resulting in gains of 1.2 ± 0.7 mm, 1.2 ± 0.8 mm, and 2.2 ± 1.1 mm for APA, CO_2 laser, and their combination, respectively.[22]

Laser versus plastic curettes, ultrasonic scaler, and titanium burs

Schwartz et al[30] reported comparable bone gain between the Er:YAG laser (1.3 ± 1 mm) and the combination of a plastic curette plus topical metronidazole (0.9 ± 0.7 mm) and had a statistically significant greater bone gain for these compared to the ultrasonic scaler (0.5 ± 0.4 mm).

5. Does the combination of chemical treatments with mechanical methods enhance reosseointegration in animal or human studies?

To determine whether the combination of chemical treatments with mechanical methods enhanced reosseointegration, studies that employed similar biomaterials and techniques while varying only the decontamination tools, specifically comparing the use of

chemical agents with mechanical methods alone or in combination with other agents, were analyzed.

Chlorhexidine
Carcuac et al evaluated the effectiveness of gauze soaked in either saline or CHX for the decontamination of various implant surfaces. While the study did not measure the percentage of reosseointegration or vertical bone gain, it assessed the residual bony defect size in histologic sections, which ranged from 1.5 to 8.9 mm^2 depending on the implant surface. The study found no significant differences in outcomes between test and control groups.[36] Schou et al reported no difference in reosseointegration between gauze soaked with CHX or citric acid (BIC 40% versus 43%), both combined with autogenous bone and ePTFE membrane.[25]

Citric acid
Almohandes et al compared the use of saline-soaked cotton pellets alone or combined with titanium brushes, titanium brushes and citric acid gel, or citric acid gel alone. While the study did not measure the percentage of reosseointegration or vertical bone gain, it assessed the radiographic bone level gain, which ranged from 0.5 to 0.7 mm. The authors reported no statistical differences between the groups, indicating that the application of citric acid had no additional effect on disease resolution.[53] Also, Schou et al observed no difference in reosseointegration whether APA was used with or without citric acid (BIC 46% versus 39%).[25] Contrarily, Htet et al reported that a titanium bur with citric acid exhibited significantly greater BIC than the titanium bur alone (8% versus 22%).[42] However, none of these studies provided data on vertical bone gain.

Hydrogen peroxide (H_2O_2)
No study assessed the effect of mechanical approaches with or without H_2O_2. It was either applied alone[44] or in combination with other chemical and mechanical approaches.[29,55]

Sodium hypochlorite
Carral et al compared the use of titanium brushes with a combination of sodium hypochlorite and CHX versus titanium brushes with CHX alone for implant surface decontamination. Both treatment groups achieved reosseointegration; however, the vertical bone gain observed was minimal, with an average of 0.2 ± 0.2 mm in both groups.[41]

Ethylenediaminetetraacetic acid (EDTA)
No studies compared the efficacy of adding EDTA to mechanical therapy.

Ex Vivo, In Situ, and In Vitro Studies

The findings from the literature review are presented in Appendix Tables 2 and 3 and are described below according to the respective questions they were designed to answer.

1. What is the impact of various decontamination methods on the presence of residual biofilm on the surface of dental implants?
Studies performed on discs may not accurately replicate the clinical scenario encountered in peri-implantitis patients, considering the micro- and macrogeometries of the implants (threads, peaks, valleys, etc) when evaluating residual biofilm. Consequently, such studies were considered unsuitable for inclusion in the present subtopic, as they do not sufficiently address the challenges associated with decontaminating implants in a clinical setting. Therefore, the focus when answering this question was specifically on studies involving implants rather than discs, and only outcomes regarding specific decontamination methods applied as the sole means of treatment were described. Results were reported using qualitative (scanning electron microscopy [SEM] images of some areas of the implant) or quantitative (colony-forming unit [CFU]) measures.

Soaked cotton pellets or gauzes
Six studies explored the efficacy of cotton pellets or gauzes as the sole method to remove biofilm from the implant surface.[62,66,90,110,127,128] In four of these studies,[62,66,127,128] this method was outperformed by other mechanical approaches, such as APA, rotating nickel-titanium brush, implantoplasty, titanium curette, Er:YAG laser, Er,Cr:YSGG laser, or water jet plus argon cold atmospheric plasma, leaving residual biofilm in subcrestal macrothreaded areas of the implants.[127] In contrast, a study involving a multispecies biofilm on 52 implants found no significant differences between APA and gauze in most cases.[110] SEM-based qualitative results from another study concluded that gauze soaked in saline and rotary stainless-steel instruments, each used independently, consistently demonstrated effective cleaning of micro- and macrothreads on both rough and machined surfaces.[90]

Plastic, carbon, titanium, and steel curettes
Four studies employed the use of curettes alone to decontaminate implant surfaces exposed in the oral cavity.[60,62,70,76] Three articles evaluated titanium curettes,[60,62,70] one plastic curettes,[60] and one study also compared titanium, plastic, and carbon curettes.[60] SEM-based qualitative results from three studies demonstrated that curettes were significantly less effective than other methods, such as APA and Er:YAG laser.[62,70,76] Conversely, one study revealed that titanium curettes

displayed superior efficacy in removing biofilm deposits compared to plastic or carbon curettes.[60]

Ultrasonic tips

One study investigated the use of ultrasonic tips as the sole method for implant decontamination and found it was less effective than three other mechanical methods (saline-soaked gauze, APA with glycine, and stainless steel rotatory brush) in terms of CFU count.[90]

PEEK

Four studies investigated the use of a PEEK ultrasonic tip alone to decontaminate the implants using qualitative measures.[60,67,70,72] Tong et al observed that the relative reduction in contaminated areas was greater in the PEEK group (83%) and PEEK plus EDTA group (83%) compared to APA (67%) and APA plus EDTA (61%).[67] Secgin-Atar et al identified clean surfaces similar to the positive control group when PEEK was utilized, as indicated by SEM using a dichotomous score (debris removed/not removed).[70] In contrast, Qian et al found an increase in the contaminated area (–154% ± 116%) due to the presence of PEEK remnants.[72] Another study reported that although cleaning with PEEK partially removed contaminants, it left behind some residual amorphous material, debris, and bacteria.[60]

Rotating brushes

Three studies employed titanium brushes assessing remaining bacterial deposits and residual live bacteria.[60,66,90] Otsuki et al showed that rotary steel instrument effectively reduced biofilm deposits by SEM evaluation. CFU analysis revealed a clinically relevant reduction from 10^7 (control) to 10^5 CFU on both rough and machined surfaces, translating to a reduction of two log scales.[90] Nevertheless, a high number of bacteria remained present, emphasizing the need for further refinement in decontamination protocols for titanium implant surfaces when rotary brushes are considered. Similarly, another study using SEM revealed incomplete removal of biofilm when rotating titanium brushes were employed.[66]

Air-powder abrasive

Fifteen studies explored the efficacy of the APA method alone to decontaminate implant surfaces.[59,63,66,67,69,71,72,76,90,107,110,112,118,119,125] Sodium bicarbonate was used in four studies,[59,66,71,119] glycine powder in three studies,[67,90,107] erythritol in six studies,[63,72,110,112,118,125] and other powders/combination in three studies.[63,69,76] Completely plaque-free implant surfaces were observed following the use of APA devices by SEM analysis in one study.[76] A successful outcome was also reported in vitro, with more than 90% of biofilm removed following the use of erythritol powder.[112] Additionally, other studies reported the presence of a thin layer of residual bacteria on the implant surface following the use of APA.[63,66,71,72,90,118,119] However, the presence of residual bacteria does not implicate viability because both viable and nonviable bacteria would appear the same under SEM. Pranno et al quantitively compared the effects of APA by means of sodium bicarbonate plus glycine powders, cotton pellets soaked in H_2O_2 and CHX, as well as both modalities combined on the decontamination of 20 failed implants prior to explantation. The concentration of viable bacteria (CFU/mL) demonstrated that no decontamination procedure achieved complete elimination of the biofilm, but APA alone or combined was more effective than the chemical-soaked cotton pellets in reducing the bacterial load.[69]

Laser therapy

A total of 10 studies evaluated the efficacy of lasers in the decontamination of implant surfaces.[60,62,65,66,68,70,73,90,98,125] Among the different types of lasers, the Er:YAG laser (2,940 nm) was the most commonly reported,[60,62,66,68,70,90] followed by Er,Cr:YSGG (2,780 nm),[62,68,70] diode (600–810 nm),[73,98,125] and neodymium-doped yttrium-aluminum-garnet (Nd:YAG) (1,064 nm)[65] or CO_2 (9,000–10,000 nm).[68]

The Er:YAG laser has demonstrated high efficacy in removing debris from the implant surface. Secgin-Atar et al reported that the Er:YAG laser long-pulse irradiation (pulse energy: 120 mJ; pulse duration: 600 µs; frequency: 10 Hz; air/water output: 4/6) effectively removed debris from the surface, similar to PEEK ultrasonic tips.[70] Linden et al[68] irradiated (20 pps, 40 to 50 mJ, water/air ratio 7/10) implants in the oral cavity prior to their removal and reported elimination of all evident bacteria on the surface as observed with SEM. Similarly, another study observed removal of residual biofilm/debris similar to APA and titanium brush (power: 1.5 W; frequency: 30 Hz; air: 40; water: 50).[66] Additionally, Er:YAG and Er,Cr:YSGG lasers irradiating at 40 mJ/pulse (ED 14.2J/cm^2/pulse) and 20 Hz with water spray in a noncontact sweeping motion were compared, and both lasers were effective in removing calculus.[62] Hakki et al found higher energy settings (200 mJ/pulse at 10 Hz) of the Er:YAG laser to be more effective in removing debris, similar to the combination of air abrasive and citric acid.[60] In contrast, Otsuki et al[90] observed that rough implant surfaces were covered with an enormous number of residuals and hence allocated the lowest value on a 4-point cleanliness scale upon laser irradiation (power setting 60 mJ/pulse, 10 pps, tip C600F), suggesting that decontamination was ineffective.

Two studies showed via SEM reduced efficacy of Er,Cr:YSGG lasers in removing debris from the implant surface compared to Er:YAG.[68,70] In contrast, another study demonstrated that both Er,Cr:YSGG and Er:YAG

lasers removed calculus effectively.[62] The efficacy of the Nd:YAG was demonstrated by Namour et al, who observed remarkable efficacy in thoroughly cleansing contaminated implant surfaces to a degree similar to a sterile implant.[65] A study using laser in combination with ultrasonic scaling prevented the ability to assess the performance of only the laser on biofilm removal.[68] Moreover, after diode laser irradiation, another study reported that the reduction in bacteria ranged from 89% to 100% and the reduction in fungi from 88% to 97%.[73] Marotti et al compared the use of a low-level diode laser alone or in combination with a dye (photodynamic therapy, PDT) with an operating mode of 660 nm, 30 mW, for 3 or 5 minutes (7.2 J and 12 J).[98] The study demonstrated better decontamination outcomes with PDT (CFU/mL was 0.6×10^3 for 5-minute PDT versus 10.6×10^3 for 5 minutes without dye irradiation) compared to untreated controls. Finally, implants were irradiated in the oral cavity before explantation by two different wavelengths of a CO_2 laser. While the wavelength of 9,300 nm still showed some dispersed aggregates of bacteria, the 10,600-nm wavelength led to greater bacterial reduction as observed by SEM.[68]

Implantoplasty

Ex vivo/in situ and in vitro studies assessing the residual bacteria after implantoplasty as a mechanical decontamination method are scarce. Only El Chaar et al assessed this method of implant decontamination ex vivo, on the surface of failed implants, in comparison to scrubbing with cotton pellets soaked with different chemical agents (saline, CHX, citric acid, phosphoric acid, H_2O_2), titanium brush, and Er:YAG laser.[66] The presence of residual bacteria was assessed by SEM using a visual index. Implantoplasty was the only method that promoted complete removal of biofilm.

Electrolytic cleaning

Electrolytic cleaning decontamination is a relatively new approach, and therefore the available evidence on this topic is still limited.[74,107,108,125,130] An in vitro study compared the efficacy of electrolytic cleaning treatment (6 V applied for 5 minutes) on implants with different surfaces to that of APA with glycine.[107] No CFUs could be counted in any group undergoing electrolytic cleaning; ie, the decontamination approach was able to inactivate the bacterial biofilm. Conversely, all control APA groups showed more than 200 CFUs. Later, another in vitro investigation of titanium-zirconium–alloy implants and sandblasted large-grit acid-etched (SLA) surfaces tested different electrical protocols applied for 5 min: 0.75 V, 1.5 V, and 3 V (anodic polarization – oxidation) and –0.75 V, –1.5 V, and –3V (cathodic polarization – reduction).[130] Significant reductions in total live bacteria counts were observed between +3 V (oxidation -1.85×10^5) and –3 V (reduction -2.92×10^4) compared to the control group (3.15×10^6), reflecting the bactericidal effect of this treatment approach. Zipprich et al compared electrolytic test protocols using either potassium iodide (KI) or sodium formate ($CHNaO_2$). Both electrolytic groups were significantly more effective for removal of both dead and live bacteria compared to APA, diode laser, and cold atmospheric plasma (CAP).[125]

Cold atmospheric plasma (CAP)

Two studies evaluated the effect of CAP.[112,125] In one study, CAP was compared to APA with erythritol or combined therapies on titanium implants incubated in saliva from a patient with peri-implantitis, and CAP alone showed the lowest biofilm removal rate (52.1%).[112] The other study reported CAP was the least effective decontamination protocol among the five studied.[125]

Chemical therapy

The use of chemical agents in the form of a gel or irrigation solution as a sole intervention has been investigated by five studies.[59,76,98,118,126] Two studies explored the use of 0.1% CHX to irrigate the surface of contaminated implants.[76,98] One study observed minimal bacterial counts (CFUs),[98] whereas the other used SEM analysis and concluded that the solution failed to remove plaque deposits, indicating its potential to kill bacteria but not effectively remove them from the surface.[76] A study using citric acid demonstrated a clean but modified surface.[59] Another study compared mechanical and chemical decontamination of implant surfaces placed in a crater-like defect model using either sulfonic/sulfuric acid gel or APA. The residual bacterial loads were significantly smaller in the acid group (CFU/mL: acid 3.1; erythritol 7.5). The percentage of reduction was 99.9% in the acid treatment group and 72.4% after APA.[118]

Combined therapies (mechanical and chemical)

Seven studies compared combined therapies to mechanical therapies alone.[66,67,71,72,75,118,127] The use of cotton pellets saturated with different chemical agents (saline, CHX, citric acid, phosphoric acid, H_2O_2) was compared to titanium brush, Er:YAG laser, and implantoplasty.[66] No additional removal of bacterial deposits was achieved by cotton pellets with chemical agents, as evaluated by SEM. Wang at al[97] observed that the combination of CHX and Er:YAG laser led to a higher percentage of dead cells (67.3%, assessed by live/dead staining on confocal microscopy) than CHX alone (43.4%) or CHX combined with PDT (56.6%). The effect of alkaline-electrolyzed water[75,127] and N-acetyl-L-cysteine[127] embedded in gauze, APA, or titanium brushes failed to improve cleaning efficacy, whereas superior decontamination of implant surfaces was reported when

ultrasonic tips, titanium brushes, and/or APA were combined with EDTA[67,72] or amino acid–buffered hypochlorite.[71] La Monaca et al reported a major reduction in the number of CFUs when APA was combined with amino acid–buffered hypochlorite in comparison to APA alone or no treatment.[71]

2. Can decontamination techniques properly clean the space between two threads (valley) on the implant surface?

The ability of different tools to clean the valley between implant threads has been examined in five articles employing ultrasonic tips, gauze soaked in saline or other chemical agent, APA, titanium brushes, water jet, and electrochemical cleaning.[67,75,90,128,130] A study emphasized that the ultrasonic tip was too large to access various parts of the implant surface.[67] Otsuki et al noted that despite the specially designed ultrasonic tip intended for cleaning contaminated implants with complex macro- and microstructures, biofilm could not be effectively removed from the microthread valleys.[90] Ichioka et al delineated three distinct regions of interest: the apex of a thread, the side of a thread (flank), and the depression between two threads (valley).[127] Their study involved chemical decontamination by rubbing gauze soaked in saline [control], alkaline-electrolyzed water, or N-acetyl-L-cysteine performed alone or in combination with APA (erythritol) or a rotating titanium brush. They observed that residual biofilm areas were more extensive at both the apex and flank compared to valley sites, with no statistically significant differences in the residual bacterial area across the various treatment groups.[127] Another study found that apically facing sites of implant threads could be sufficiently reached by a water jet but not by cotton gauze.[128] Virto et al identified low amounts of bacterial cells both at the thread peaks and within the valleys after using different electrochemical regimens.[130]

3. Can decontamination techniques have adverse effects on the implant surface?

To address this question, studies involving both implants and discs were included. Adverse effects were defined as any alterations in surface topography, including scratches, cracks, or remnants of the decontamination tool. To accurately attribute these adverse effects to specific decontamination methods, only studies reporting outcomes on specific decontamination methods when utilized as the sole means of treatment were analyzed.

Soaked cotton pellets or gauze

Five studies showed that after treatment using cotton pellets or gauze soaked in saline, the microstructured surface of the implants was preserved.[62,100,110,127,128] One article reported that gauze remnants occasionally remained on implant surfaces after treatment.[127]

Plastic, carbon, titanium, and steel curettes

Six investigations demonstrated that utilizing either titanium or steel curettes resulted in notable surface alterations and flattening of implant peaks.[62,70,83,86,129,131] Additionally, one study assessed SEM images and showed that residues of plastic and carbon were evident when employing plastic and carbon curettes, respectively, while the utilization of titanium curettes left behind minimal residues.[60]

Ultrasonic tips

Of five studies[102,106,123,129,132] where ultrasonic tips were employed to decontaminate implants or discs, three investigated whether any surface changes occurred during treatment.[102,129,132] Plaque-coated discs treated with an ultrasonic scaler with a metal tip showed a markedly flattened surface with scraping grooves and the disappearance of microcavities, but with incomplete removal of the titanium dioxide (TiO_2) layer and scant aggregates.[102] Similarly, the use of an ultrasonic scaler with a titanium tip resulted in significant alterations across all surfaces, including formation of grooves on smooth surfaces and flattening of projections on both abraded and SLA surfaces.[129] Recently, Zhu et al observed that ultrasonic scalers altered the SLA surface of titanium discs in varying degrees, leaving chunky scratches.[132]

PEEK

Four studies studied the effect of PEEK on the implant surface.[60,67,70,72] All reported no surface alterations but observed material remnants on the implant surface after decontamination. Accordingly, one study performed on discs reported the presence of 20- to 80-µm-sized flakes that were considered residual PEEK remnants.[132]

Rotating brushes

Ten studies evaluated the surface integrity of implants or discs following the use of rotatory brushes.[60,83,86,113,122,123,129,131,132] Extracted implants treated with eight different procedures showed surface alterations characterized by flat or partially disfigured topography.[60] Tran et al compared nickel-titanium brushes to APA, ultrasonic titanium tips, curettes, and citric acid. The brush produced the most pronounced surface alterations and significant modifications to the implant topography, including scratching and flattening of projections, particularly on SLA discs.[129] The use of a rotating titanium brush led to an elevated release of titanium particles[131] and mechanical surface alterations of the titanium surfaces with titanium brush streaks visible under atomic force microscopy as "valleys" and

pits.[113] These changes were linked to the generation of titanium wear microparticles as a direct effect of cleaning, whereas the same study observed that nylon brush and water jet were the least aggressive intervention with surface patterns consistent with no surface mechanical abrasion.[113] Zhu et al also reported varying degrees of surface alterations following the use of titanium brushes, leaving the SLA surface full of strips.[132]

Air-powder abrasive

Eighteen studies evaluated the effect of APA devices on titanium surfaces.[59,60,63,67,72,76,79,81,87,95,110-112,119,123,127,129,132] Some reports indicated the absence of powder deposition on the surface[60,79] or the absence of significant alterations in surface microtopography.[60,76,95,111,112,119,127,132] Two studies reported residuals of PEEK but not glycine or erythritol powder remnants.[67,72] In contrast, few articles observed the presence of small amounts of contaminants/residual powder on the surface of implants.[59,63,110,132] Studies performed on discs observed similar findings of clusters of powder particles covering the titanium surface following the use of APA.[63,81,87] Small alterations on the titanium surface, such as flattening of the sharp edges following the use of sodium bicarbonate, glycine, hydroxyapatite, calcium and tricalcium phosphate, phosphate, titanium dioxide, or combinations were also reported.[81,87] In the in vitro comparison of different powders—glycine, calcium carbonate, and sodium bicarbonate, with average particle sizes of 25 µm, 55 µm, and 76 µm, respectively—on three titanium surfaces (smooth, abraded, and SLA), distinct surface changes were observed with the more abrasive powders. Glycine powder did not induce discernible surface alterations to any of the three surfaces studied. Sodium bicarbonate neither scratched the smooth surface nor caused discernible changes to abraded surfaces, but it occasionally left abrasive particles embedded and caused some minor change to the SLA surface. Conversely, calcium carbonate left embedded abrasive particles and scratch marks into the smooth surface, smoothing over of projections on abraded surfaces, as well as flattening of the projections and roughness of the SLA surface.[129]

Laser therapy

A total of 13 studies[59,62,64,65,68,70,73,77,86,93,102,123,131] evaluated adverse effects of lasers on titanium surfaces, most of which involved Er:YAG lasers.[62,64,68,70,73,86,93,102,123,131] No signs of melting were reported by most studies evaluating Er:YAG, Er,Cr:YSGG, Nd:YAG, or diode lasers.[62,64,65,73,77] Contrasting outcomes were reported by Linden et al for the Er,Cr:YSGG laser.[68] Decontamination of implants prior to explantation with *(1)* ultrasonic tips plus Nd:YAG , *(2)* Er,Cr:YSGG, *(3)* Er:YAG, *(4)* CO_2 with 9,300 nm, or *(5)* CO_2 with 10,600 nm, respectively, was compared. Small areas of localized surface alterations and porous globules were visible on the implant surfaces irradiated with the Er,Cr:YSGG laser, indicating melting and resolidification of bone hydroxyapatite mineral along with melting and increasing porosity of the implant surface.[68] Melting was also reported for the Er:YAG laser in specific settings (70 or 100 mJ/pulse).[93] In the study performed by Giannelli et al, Er:YAG laser irradiation (38.2 J/cm^2 for 1 min) led to complete stripping of plaque and the TiO_2 layer, resulting in a micropitted surface with no signs of melting or heat-induced deformation.[102] Similarly, Costa et al observed an overall polished appearance with reduced sharpness of the peaks, while the valley areas appeared unaffected after irradiation with Er:YAG (40 mJ, 0.80 W, 20 Hz, in continuous mode).[131] Another study demonstrated that very-short or short-pulse Er:YAG laser irradiation led to more alterations to the surface than an Er,Cr:YSGG laser. Delamination and deformation of the surface, porosity due to melting, loss of honeycomb appearance, and a relatively smooth surface with microcracks were observed. On the other hand, a study demonstrated that Er:YAG laser irradiation in long-pulse mode (600 µs) preserved a surface topography comparable to the original SLA implant surface, with no visible alterations under SEM, and demonstrated superior cleanliness compared to the Er,Cr:YSGG laser.[70] Lastly, a CO_2 laser without a photosensitizing agent left burned tissue debris attached to the surface.[59]

Implantoplasty

The implantoplasty procedure is conducted with the aim of smoothing or reshaping the surface of dental implants; as such, an intentional alteration of the implant's structure occurs. Research on surface damage during implantoplasty with implants previously contaminated by biofilm has not been reported.

Electrolytic cleaning

A study demonstrated that the application of electrolytic cleaning treatment to titanium surfaces yielded minimal alterations in surface roughness but led to increased oxidation of the titanium metal and subsequent thickening of the oxide layer.[85] Similarly, another study reported no titanium surface alterations.[132]

Cold atmospheric plasma

Interpreting SEM imaging at various magnifications revealed no discernible post-CAP treatment surface alterations, such as crater-like defects or scratches.[111,112]

Chemical therapy alone

Two studies evaluated surface alterations following the application of chemical agents exclusively.[59,76] One study reported no damage after CHX solution was

Table 1 Summary of Evidence

Animal and human biopsy studies	
Is implant reosseointegration possible after the treatment of peri-implantitis?	Animal and human biopsy studies suggested that implant reosseointegration is possible following appropriate surface decontamination.
Which mechanical decontamination methods demonstrated reosseointegration in animal or human studies	APAs were the most frequently investigated method, featured in 8 studies. Seven studies demonstrated successful reosseointegration (BIC and VBG). Laser therapy was evaluated in 5 studies. Two studies (Er:YAG and CO2 lasers) reported successful reosseointegration (BIC and VBG), while two reported modest results (Er:YAG and diode lasers) and 1 only reported that reosseointegration was achieved (Er,Cr:YSGG laser). Cotton pellets were analyzed in 4 studies. Two studies reported successful reosseointegration, whereas the other two demonstrated a failure of reosseointegration. Curettes were examined in two studies (plastic and carbon curettes), which showed modest results in BIC and VBG. Ultrasonic devices were examined in a single study, which yielded limited results for BIC and VBG. Electrolytic cleaning was examined in only one study, which reported variable outcomes in BIC and successful VBG. Evidence supporting the use of implantoplasty, PEEK ultrasonic tips, and titanium brushes as individual decontamination tools were absent.
Has any decontamination method shown superior histologic vertical bone gain (mm) in animal or human studies?	None of the methods examined demonstrated a clinically significant superiority in terms of reosseointegration and VBG among studies that utilized the same biomaterials and techniques but varied in decontamination tools.
Does the combination of chemical treatments with mechanical methods enhance reosseointegration in animal or human studies?	Among studies using the same biomaterials and techniques, evidence—though limited—indicates that chemical treatments do not significantly improve BIC or VBG compared to mechanical methods alone.
Ex vivo, in situ, and in vitro studies	
What is the impact of various decontamination methods on the presence of residual bacteria on the surface of dental implants?	Great biofilm removal was observed when PEEK, APA, Er:YAG laser, and electrolytical cleaning were employed. Lower biofilm removal rates were observed when cotton pellets or gauze, plastic curettes, or cold atmospheric plasma were used. The evidence was very limited for titanium curettes, ultrasonic tips, rotating brushes, and implantoplasty as methods for decontamination as well as for the advantages of combining mechanical and chemical therapies.
Can decontamination techniques properly clean the space between two threads (valley) on the implant surface?	The monotherapeutic use of mechanical instruments, such as ultrasonic tips and curettes, has limitations when attempting to clean intricate areas like the valleys between dental implant microthreads. The size of their tips may be too large to effectively access these smaller spaces. Mechanical decontamination with cotton gauze may not reach apically facing sites of implant threads. Approaches utilizing waterpower and electrochemical appear to have a better capacity for cleaning these valleys and may offer improved efficacy in reaching and cleaning these challenging areas.
Can decontamination techniques have adverse effects on the implant surface?	Minimal surface alterations were observed following the use of cotton pellets, APAs, Er:YAG laser with specific settings (<70 mJ/pulse), Er,Cr:YSGG laser, electrochemical treatment, and cold atmospheric plasma. Titanium or stainless steel curettes, ultrasonic tips, and titanium brushes led to notable surface alterations and flattening of peaks. Er:YAG laser irradiation with specific settings (≥ 70 mJ/pulse) led to surface melting. Implantoplasty led to intentional modification of the implant surface. Plastic and carbon curettes as well as PEEK ultrasonic tips left material remnants. APAs could leave clusters of powder particles covering the titanium surface if utilized with low water flow.

VBG = vertical bone gain (histologic).

applied,[76] while the other observed nonreflecting spots covering a large part of the implant surfaces following application of citric acid.[59]

Combined therapies (mechanical and chemical)

Three studies compared surface alterations by mechanical therapy alone to mechanical and chemical therapies combined.[67,72,95] EDTA combined with ultrasonic PEEK and APA significantly decreased implant roughness, promoting a surface similar to a sterile implant,[67,72] and removed PEEK remnants from the implant surface.[67,72] Lollobrigida et al assessed the effects of titanium brushes or APA combined with sodium hypochlorite or citric acid. No significant alterations were observed to the implant surfaces besides the original mechanical approaches. Nevertheless, sodium hypochlorite dissolved residual bacterial cells to a greater extent than citric acid, while citric acid seemed to be more effective in dissolving residual organic debris after APA treatment.[95]

4. What is the biologic response of implant surfaces to different decontamination methods in cell culture models?

- Several studies evaluated the biologic response of implant surfaces following decontamination, specifically focusing on osteoblast attachment, proliferation, and cytocompatibility, as shown in Appendix Tables 2 and 3.
- APA systems, particularly those using erythritol or glycine powders, demonstrated favorable outcomes across multiple in vitro models. Tastepe et al[104] reported up to a sixfold increase in osteoblast-like cell viability compared to contaminated controls on titanium disks treated with erythritol-based APA. Similarly, Matthes et al[103] reported that APA, when used alone or in combination with CAP, resulted in 57.5% to 84.7% viable osteoblast coverage after 5 days of culture, with enhanced wettability and low cytotoxicity. John et al[87] further confirmed that bicarbonate and glycine-based APA did not impair cell viability or attachment on either titanium or zirconia surfaces. Schwarz et al[79] and Lollobrigida et al[95] also further supported the cytocompatibility of APA-treated surfaces in in situ models, with Lollobrigida reporting higher osteocalcin release on machined surfaces.[95]
- Titanium brushes used alone provided moderate cytocompatibility. Jin et al[106] reported well-attached osteoblasts on treated surfaces, but the cytocompatibility varied depending on the brush material and implant surface type. Lollobrigida et al[95] observed reduced osteoblastic activity on SLA surfaces treated with titanium brushes, particularly when combined with NaOCl. In contrast, Sousa et al[122] demonstrated that titanium disks treated with a titanium brush in combination with UV-C radiation, photodynamic therapy, or CHX/NaOCl supported significantly improved osteoblast-like cell proliferation relative to mechanical treatment alone. These surfaces also exhibited higher oxygen and lower carbon content, suggesting improved surface chemistry conducive to cell attachment.
- Laser-based treatments, particularly the Er:YAG laser, consistently supported enhanced cell adhesion. Eick et al[102] reported increased epithelial and osteoblast adherence following Er:YAG decontamination compared to mechanical methods. Giannelli et al[102] found that higher energy settings (38.2 J/cm2) achieved superior plaque removal and osteoblast compatibility, whereas lower energy (20.3 J/cm2) was associated with residual contamination and diminished cell response.
- None of the reviewed studies evaluated cytocompatibility or osteoblast behavior on treated surfaces using electrolytic cleaning.
- CAP also contributed positively to surface biocompatibility. Matthes et al[121] and Duske et al99 observed improved surface wettability and dense osteoblast coverage when CAP was applied, particularly in conjunction with mechanical cleaning. In these studies, cell coverage of up to 82% was reported.
- Chemical agents yielded variable results. Kotsakis et al[100] showed that CHX was associated with the lowest osteoblast viability, while EDTA and NaOCl demonstrated more favorable outcomes, particularly on roughened surfaces. Han et al[105] reported minimal differences in osteoblast morphology across groups treated with citric acid, CHX, or hydrogen peroxide. Lollobrigida et al[95] reported reduced osteoblast proliferation and poor adhesion on SLA surfaces treated with NaOCl, regardless of the mechanical method used.
- Overall, the most favorable cell culture outcomes were observed with APA systems, Er:YAG lasers, CAP, and combined protocols involving titanium brushes and UV-C. Chemical agents, particularly CHX, may impair osteoblastic responses when used in isolation.

Summary of Evidence

Table 1 provides a comprehensive summary of the evidence addressed in the present review.

DISCUSSION

Clinical Remarks Based on Results from Animal and Human Biopsy Studies

The knowledge obtained from animal studies highlights the pivotal importance of local therapy and implant decontamination in treating peri-implantitis lesions. Our review shows that systemic antibiotics without the inclusion of local therapy are ineffective in eliminating peri-implantitis lesions. The available evidence shows that implant reosseointegration is possible following appropriate surface decontamination. Among the various tools investigated, reosseointegration outcomes were most frequently reported with the use of APA and laser, whereas evidence for implantoplasty, PEEK ultrasonic tips, and titanium brushes as individual decontamination tools was lacking. Nevertheless, establishing a gold standard decontamination method remains challenging due to the limited number of studies using the same biomaterials and techniques while varying decontamination tools, with none of them demonstrating clinically significant superior outcomes.

In line with Waerhaug's (1977)[133] observation of a plaque-free zone that separates the inflammatory infiltrate from the bone around teeth, Ericsson et al described a 1-mm-wide connective tissue zone that separates the plaque/inflammatory infiltrate from the bone around implants.[134] This concept may be key to understanding reosseointegration, particularly in studies that reported minimal vertical bone gain. If the bottom portion of the infrabony defect was a plaque-free zone, the reported "reosseointegration" may have occurred in an area that was not previously contaminated by plaque, implying that the decontamination tool may not have influenced the outcome.[135] Consequently, the clinical significance of studies reporting reosseointegration of less than 1 mm in height may be questionable.[135] In the present review, out of 25 studies that reported this outcome (22 animal, 3 human), 19 studies presented at least one group with vertical bone gain exceeding 1 mm,[15,16,22,24,29,30,35,38–40,44–47,49,52,55,56,58] while 7 studies demonstrated vertical bone gain greater than 2 mm.[15,16,22,39,44,52,58]

Despite the focus of this study being decontamination methods, the following clinical conditions beyond implant decontamination may have influenced the healing and interpretation of the included studies in the establishment of BIC and might dictate some differences when translated to clinical practice.

Implant surfaces

With their unique chemical compositions and varying surface free energies, the high variability of commercially available implant surfaces appears to play a significant role in determining the amount of histometric BIC and bone gain after treatment.[28,29,31,37,47,53]

Geometry of infrabony defects

The geometry of the defects significantly influences clot stability. While most defects in canine models are circumferential (1E) according to Schwartz et al,[136] defects resulting from peri-implantitis may be noncontained or horizontal[11] and are likely to heal with the formation of a soft tissue interface rather than bone in contact with the treated implant surfaces.[136] Moreover, implant position within the bone may also influence infrabony defect morphology and, despite decontamination efforts, may obviate achieving reosseointegration.[137]

Bone graft and membrane

Studies have demonstrated a positive correlation between the placement of bone graft materials within bony defects and an increase in BIC.[26,27,45,47] This observed enhancement in BIC is likely attributable to the osteoconductive potential of the graft material acting as an effective scaffold to support new bone growth and integration around the implant. Placing a membrane to cover/contain the graft material provides space maintenance, which has been shown to enhance the extent of bone regeneration.[13,26]

Premature barrier exposure

Early membrane exposure can adversely affect bone healing and regeneration around implants treated with guided bone regeneration. This is notably observed in dog models in which premature exposure of ePTFE membranes allowed bacteria to access the underlying tissues, perpetuating an inflammatory response around implants.

Nonsubmerged versus submerged healing

Consistently, submerged healing resulted in greater vertical bone gain and increased BIC compared to nonsubmerged healing.[13,22,30] The submersion of the defect and biomaterial may provide temporary protection of the peri-implant wound area against pathogenic bacteria from the oral cavity, as well as improved clot stability.

Clinical Remarks Based on Results from Ex Vivo, In Situ, and In Vitro Studies

When exploring options for an effective decontamination tool, researchers aim to find a method capable of thoroughly eliminating bacteria and clearing debris from every aspect of the implant surface without promoting alterations to the surface or leaving residues from instruments. Biofilm removal is the foundation of implant surface decontamination.[138] Mechanical debridement with hand curettes has been advocated as a preferred clinical alternative.[139] Our findings, however, challenge this recommendation, indicating that plastic curettes may be less effective in biofilm removal. These tools face limitations when attempting to clean

areas like the apical implant flanks and valleys between threads on implants. The dimension of the ultrasonic tip may be too large to effectively access these smaller spaces. Consequently, tools routinely employed for periodontitis management do not exhibit the same efficacy in addressing peri-implantitis. The other tools studied in this review demonstrated the ability to remove greater amounts of bacteria. Furthermore, it is important to emphasize that complete removal of biofilms and debris seems to be neither achievable nor necessary to achieve reosseointegration.[58]

Apart from APA, Er:YAG laser (< 70 mJ/pulse), Er,Cr:YSGG laser, electrochemical treatment, and cold atmospheric plasma, other mechanical protocols led to alterations on implant surfaces. Titanium or stainless steel curettes, ultrasonic tips, and titanium brushes led to notable surface alterations and flattening of peaks. Er:YAG laser irradiation (≥ 70 mJ/pulse) led to surface melting. Plastic and carbon curettes, PEEK ultrasonic tips, and APA left material remnants. Implantoplasty led to intentional modification of the implant surface. While the potential consequences of surface damage during bone regeneration attempts remain unclear, concerns regarding potential titanium degradation with mechanical means, especially instrumented surfaces, have been prominently highlighted in the literature.[140] Despite the incomplete understanding of the cause-effect relationship between titanium dissolution and peri-implant diseases, titanium subproducts have been linked to complex inflammatory responses[141] and microbial dysbiosis.[142] The cumulative release of titanium subproducts from the surface warrants further investigation to assess potential harm to the peri-implant tissues and to the structural integrity of implant surfaces. In addition to surface deterioration, mechanical instrumentation has the potential to disrupt the oxide film naturally forming on titanium-based implants, inducing oxidation and active material surface attack.[8] Previous systematic reviews[5,143] have demonstrated the superior cleaning potential of rotating titanium brushes over other decontamination methods, but the irreversible surface damage and titanium release observed in our study question the viability of the titanium brush approach.

When interpreting the results of the present review, it is crucial to recognize the distinctions between the controlled laboratory setting of implant surface decontamination and the dynamic clinical environment of peri-implantitis surgical therapy. Accessibility to implants affected by peri-implantitis varies significantly due to factors such as defect configuration, the position of the implant in the mouth, and the presence/absence of infrabony defects. Subanalysis of both the intrabony defect and the supracrestally located surface areas should be conducted to examine the accessibility of various instruments within the confined infrabony region. Therefore, these contextual differences must be considered when drawing conclusions from the study findings since only two of the studies in this review decontaminated the implants in the mouth before explantation and subsequent analysis of residual bacteria/biofilm and surface alterations.[69,71]

CONCLUSIONS

- Decontamination of the implant surface is necessary to resolve a peri-implantitis lesion.
- Implant reosseointegration is possible following appropriate surface decontamination. However, none of the methods examined demonstrated a clinically significant superiority in terms of reosseointegration and vertical bone gain among studies that utilized the same biomaterials and techniques but varied in decontamination tools.
- Evidence from animal and human biopsy studies suggests that the local application of chemical treatments in combination with mechanical methods does not significantly enhance BIC or vertical bone gain compared to mechanical methods alone.
- Ex vivo, in situ, and in vitro studies demonstrated greater biofilm removal with the use of PEEK, APA, Er:YAG laser, and electrolytical cleaning.
- Minimal surface alterations were noted following the use of cotton pellets, APAs, Er:YAG laser (< 70 mJ/pulse), Er,Cr:YSGG laser, electrochemical treatment, and cold atmospheric plasma. In contrast, other instruments led to surface alterations and flattening of peaks or left material remnants.
- An ideal decontamination protocol aims to completely eradicate biofilm from all surfaces of the implant while avoiding the release of titanium particles, preventing any alterations to the implant's macro and micro surfaces, and minimizing residual traces from the decontamination tools. In this context, electrolytic cleaning, APA, and Er:YAG laser therapy emerged as methods that best embody the attributes of effectiveness.

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A.R. and P.S.R. designed the study; A.R., D.D., R.L., and M.B. performed the literature search, initial screening, and record selection and extracted the data and assessed the risk of bias; A.R., D.D., and M.B. led the writing; and R.L. and P.S.R. revised the manuscript.

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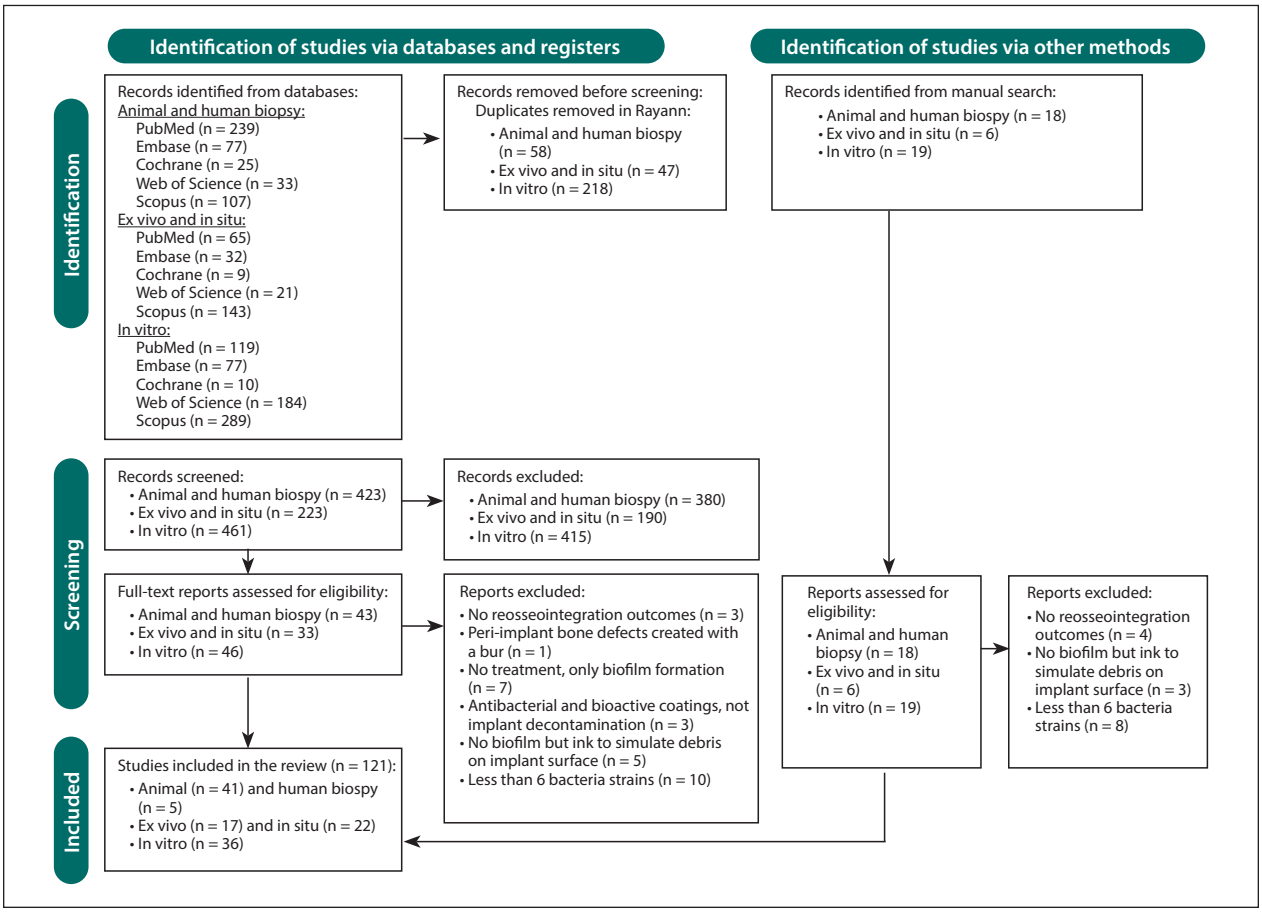
APPENDIX



Appendix Fig 1 Electronic and manual search and results.

Appendix Table 1 Biofilm Decontamination and Reosseointegration of Titanium Implants: Animal and Human Block Biopsy Studies

Study	No. of animals, no. and kind of implants, and surface	Peri-implantitis model	Decontamination method
Animal studies			
Grunder et al[11] (1993)	10 dogs 40 MTX	Cotton floss ligature (5 mos)	APA (bicarbonate
All references refer to main article reference list.			
Jovanovic et al[12] (1993)	3 dogs 21 pure Ti, TPS, or HA-coated	Silk ligature (3 mos)	APA (bicarbonate) and citric acid
Singh et al[13] (1993)	2 micropigs 12 implants (N/A)	Silk ligature (6 weeks)	APA (n/a)
Ericsson et al[14] (1996)	5 dogs 30 TiUnite	Cotton floss ligature (2 mos)	Systemic amoxicillin + metronidazole and: 1) Delmopinol hydrochloric acid 1% solution 2) Untreated
Hanisch et al[15] (1997)	4 monkeys 32 TPS	Cotton floss ligature (10 mos)	APA (bicarbonate) and citric acid
Hürzeler et al[16] (1997)	7 dogs 42 TiUnite	Silk ligature (3 mos)	APA (bicarbonate)
Machado et al[17,18] (1999, 2000)	4 dogs 16 pure Ti	Cotton floss ligature (1 mo)	APA (bicarbonate)
Persson et al[19] (1999)	4 dogs 24 TiUnite	Cotton floss ligature (3 mos)	1) Rotating brush with abrasive pumice 2) Saline-soaked cotton pellets
Wetzel et al[20] (1999)	7 dogs 34 implants a) ALA b) TPS c) Machined surface	Silk ligature (4 mos)	SS CUR and 0.12% CHX irrigation
Nociti et al[21] (2000)	5 dogs 20 acid-etched surface	Cotton floss ligature (1 mo)	APA (bicarbonate)

Regenerative therapy groups	Healing type (duration)	Histologic outcomes	
		Reosseointegration (BIC ± SD%)	Vertical bone gain (mm ± SD; fBIC to BD)
1) Submerged only 2) Submerged with ePTFE membrane 3) Nonsubmerged only 4) Nonsubmerged with ePTFE membrane	Submerged; nonsubmerged (3 mos)	Achieved (N/A)	Absolute (mm) 1) –0.1 (± 0.1) 2) 0.3 (± 0.2) 3) –0.1 (± 0.2) 4) 0.2 (± 0.1)
ePTFE membrane	Submerged (2–4.5 mos)	Achieved (N/A)	N/A
1) Nonsubmerged 2) Submerged 3) ePTFE and submerged	Submerged; nonsubmerged (3 mos)	BD – 2nd thread 1) None 2) 7.8 3) 35.6	N/A
No graft No membrane	Nonsubmerged (4 mos)	None	N/A
1) BMP in collagen sponge (test) 2) Collagen sponge (control)	Nonsubmerged (4 mos)	BD – IS 1) 29 (± 10.5) 2) 3.5 (± 2.5) BD – fBIC 1) 40 (± 11) 2) 8.9 (± 7.8)	Absolute (mm) 1) 2.6 (± 1.2) 2) 0.8 (± 0.8)
1) No graft 2) Resorbable HA 3) Canine DFDBA 4) ePTFE 5) HA and ePTFE 6) Canine DFDBA and ePTFE	Submerged (4 mos)	Achieved (N/A)	Absolute (mm) 1) 0.3 (± 0.3) 2) 0.9 (± 0.4) 3) 0.9 (± 0.3) 4) 1 (± 0.2) 5) 2.3 (± 0.6) 6) 2.2 (± 0.4)
1) No graft 2) PTFE membrane 3) Bone XG 4) PTFE and XG	(5 mos)	6 most coronal threads 1) 26.9 2) 30.7 3) 28.1 4) 27.2	N/A
No graft	Submerged (3 mos)	Achieved (minor amounts – considered failure)	Absolute (mm) 1) 0.4 (± 0.1) 2) 0.4 (± 0.1)
1) No ePTFE 2) ePTFE membrane	Submerged (6 mos)	Achieved (N/A)	Absolute (mm) 1a) 0.3 (± 0.2) 1b) 0.3 (± 0.5) 1c) 0.2 (± 0.2) 2a) 0.6 (± 0.3) 2b) 0.5 (± 0.3) 2c) 0.07 (± 0.1) Relative (%) 1a) 11.1 1b) 13.9 1c) 7.1 2a) 19.7 2b) 13.6 2c) 2
1) No graft 2) Collagen membrane 3) Bone XG 4) Bone grafting and collagen membrane	(5 mos)	6 most coronal threads 1) 26.9 2) 26.7 3) 28.1 4) 25.6	N/A

Appendix Table 1 *(cont)* **Biofilm Decontamination and Reosseointegration of Titanium Implants: Animal and Human Block Biopsy Studies**

Study	No. of animals, no. and kind of implants, and surface	Peri-implantitis model	Decontamination method
Deppe et al[22] (2001)	6 dogs 60 TPS	Ligature (3 mos)	1) APA (n/a) 2) CO_2 laser 3) APA and CO_2 laser
Persson et al[23] (2001)	2 dogs 22 implants 1) TiUnite 2) Two-piece TiUnite	Cotton floss ligature (3-4 mos)	Saline-soaked cotton pellets
Persson et al[24] (2001)	4 dogs 24 implants 1) Machined 2) SLA	Cotton floss ligature (3 mos)	Saline-soaked cotton pellets
Schou et al[25,26] (2003)	8 monkeys 64 TPS	Silk ligatures; orthodontic elastics (9–18 mos)	1) APA (bicarbonate) and citric acid 2) APA (bicarbonate) 3) Gauze soaked in saline and citric acid 4) Gauze soaked in CHX and saline
Schou et al[27] (2003)	8 monkeys 64 TPS	Silk ligatures; orthodontic elastics (9–18 mos)	Gauze soaked alternately in 0.1% CHX and saline solutions and irrigation with both
Shibli et al[28] (2003)	6 dogs 36 implants: 1) cpTi 2) HA 3) Ti plasma-sprayed 4) Machined and acid etched	Cotton floss ligature (3 mos)	Saline irrigation and PDT (diode laser)
Persson et al[29] (2004)	4 dogs 24 implants SLA Turned	Cotton floss ligature (3 mos)	1) CO_2 laser and H_2O_2 (10 mm) 2) Saline-soaked cotton pellets
Schwarz et al[30] (2006)	5 dogs 30 SLA	Cotton floss ligature (3 mos)	1) Er:YAG laser 2) US 3) Plastic CUR and topical metronidazole
Shibli et al[31] (2006)	5 dogs 40 cpTi, TPS, oxide, or acid	Cotton floss ligature (3 mos)	1) Plastic CUR 2) Plastic CUR and saline rinse and diode laser
You et al[32] (2007)	6 dogs 36 cpTi; rough surface	Gauze; wire (N/A)	Gauze soaked alternately in 0.1% CHX or saline solution

Regenerative therapy groups	Healing type (duration)	Histologic outcomes	
		Reosseointegration (BIC ± SD%)	Vertical bone gain (mm ± SD; fBIC to BD)
No graft 4 quadrants each: a) 3 ePTFE membrane b) 1 no membrane	Submerged; nonsubmerged (4 mos)	Achieved (N/A)	Absolute (mm) 1a) 1.2 (± 0 .7) 2a) 1.2 (± 0.8) 3a) 2.2 (± 1.1) 1b) 0.6 (0.6) 2b) 0.6 (± 0.5) 3b) 0.7 (± 0.5)
No graft	Submerged (4 mos)	Achieved (minor amounts – considered failure)	Absolute (mm) 1) 0.3 (± 0.2) 2) 0.3 (± 0.2)
No graft	Nonsubmerged (6 mos)	BD – fBIC 1) 67.6 (± 1 0.3) 2) 62.9 (± 2.1)	Absolute (mm) 1) 0.4 (± 0.1) 2) 1.2 (± 0.3) Relative (%)
Autogenous bone and ePTFE	Nonsubmerged (6 mos)	BD – fBIC (point counting) 1) 46 2) 39 3) 43 4) 40	N/A
1) XG bone and PTFE membrane 2) XG bone 3) PTFE membrane 4) No graft, no membrane	Nonsubmerged (6 mos)	BD – fBIC 1) 36 2) 23 3) 21 4) 13	N/A
No graft; ePTFE membrane	Submerged (5 mos)	BD – IS 1) 24.9 (± 17.7) 2) 15.8 (± 9.6) 3) 25.2 (± 11.9) 4) 17.3 (± 15.4)	N/A
No graft	Nonsubmerged (6 mos)	BD – fBIC 1a) 72.1 (± 12) 2a) 62.9 (± 2) 1b) 59.3 (± 8) 2b) 67.6 (± 10)	Absolute (mm) 1a) 1.1 (± 0.3) 2a) 1.2 (± 0.3) 1b) 0.5 (± 0.1) 2b) 0.4 (± 0.1) Relative (%) 1a) 74 (± 3 0) 2a) 84 (± 9) 1b) 21 (± 9) 2b) 22 (± 17)
No graft	Submerged (3 mos)	BD – fBIC 1) 44.8 2) 8.7 3) 14.8	Absolute (mm) 1) 1.3 (±1) 2) 0.5 (± 0.4) 3) 0.9 (± 0.7)
No graft	Submerged (5 mos)	BD – IS 1) 8.4 (± 11.2) 2) 37.1 (± 19)	N/A
1) Autogenous bone graft particles with platelet-enriched fibrin glue 2) Autogenous bone graft particles 3) No graft	(6 mos)	3 most coronal threads 1) 50.1 (± 14) 2) 19.3 (± 8) 3) 6.5 (± 7)	N/A

Appendix Table 1 *(cont)* **Biofilm Decontamination and Reosseointegration of Titanium Implants: Animal and Human Block Biopsy Studies**

Study	No. of animals, no. and kind of implants, and surface	Peri-implantitis model	Decontamination method
Parlar et al[33] (2009)	9 dogs 54 machined, SLA, or TPS	Cotton floss ligature (3 mos)	1) Intraosseous cylinder removal and exchange 2) Pressurized saline with air-polishing device 3) Intraosseous cylinder removal and pressurized saline with air-polishing outside the oral cavity and remount
Albouy et al[34] (2011)	6 dogs 48 implants 1) Turned 2) TiOblast 3) SLA 4) TiUnite	Cotton floss ligature (4 mos)	Sterile saline-soaked gauze and CURs
Schwarz et al[35] (2011)	6 dogs 48 SLA	Cotton floss ligature (4 mos)	Plastic CURs and sterile saline-soaked cotton pellets
Carcuac et al[36] (2015)	6 dogs 20 implants TiOblast surface, Osseospeed surface and AT-I surface	Cotton floss ligature (2 mos)	1) Sterile saline-soaked gauze 2) CHX-soaked gauze
Namgoong et al[37] (2015)	5 dogs 30 implants 1) Turned 2) SA 3) SA and HA	Wire ligature (6 mos)	CHX-soaked cotton pellets
Park et al[38] (2015)	6 dogs 24 sandblasted with alumina and acid etched	Wires (4 mos)	1) Irrigation with syringe with sterile saline 2) Dental water jet 3) Dental water jet and floss
Park et al[39] (2015)	6 dogs 24 sandblasted with alumina and acid etched	Cotton floss floss ligature (4 mos)	1) Irrigation with syringe with sterile saline 2) Dental water jet 3) Dental water jet and floss Dental water jet and CHX-soaked dental floss
Shi et al[40] (2015)	6 dogs 12 sandblasted surface of HA and β-TCP	Cotton floss ligature (until 40% bone loss)	CHX and sterile saline solution irrigation
Carral et al[41] (2016)	8 dogs 48 TiZr implants SLA	Silk ligature (3 mos)	1) TiB and NaOCl 0.1% and CHX 0.2% 2) TiB and CHX 0.2% 3) Plastic tip of US and CHX 0.2% 4) No treatment

Regenerative therapy groups	Healing type (duration)	Histologic outcomes	
		Reosseointegration (BIC ± SD%)	Vertical bone gain (mm ± SD; fBIC to BD)
No graft; collagen membrane	Submerged (3 mos)	All implant body Mean 1, 2, and 3) 62.3 (± 18.2)	Implant apex to fBIC 1) 6.8 2) 8.2 3) 7.2
No graft	Nonsubmerged (5 mos)	N/A	N/A
1) XG bone and equine bone blocks and collagen membrane 2) XG bone and implantoplasty and collagen membrane 3) XG bone and rhBMP-2 and equine bone blocks and collagen membrane 4) XG bone mineral and rhBMP-2 and implantoplasty and collagen membrane	Submerged (4 mos; nonexposed sites)	BD – IS 1) 19.7 (± 9.4) 2) 15 (± 11) 3) 28 (± 18.1) 4) 32.1 (± 27.8)	Absolute (mm) 1) 1.1 2) 0.8 3) 1.7 4) 1.7 Relative (%) 1) 20.1 (± 8) 2) 19 (± 15) 3) 34.4 (± 17) 4) 38.1 (± 26)
No graft	Nonsubmerged (6 mos)	N/A	N/A
Collagen membrane, no graft	Submerged (4 mos)	BD – fBIC 1) 40.3 (± 44) 2) 49.8 (± 39) 3) 60.9 (± 39)	Absolute (mm) 1) 0.1 (± 0.2) 2) 0.5 (± 0.7) 3) 0.5 (± 0.6)
XG and collagen membrane	(3 mos)	BD – fBIC 1) 55.6 (± 33) 2) 67.2.6 (± 38) 3) 57 (± 32.8)	Absolute (mm) 1) 0.3 (± 0.1) 2) 1 (± 1.2) 3) 1.8 (± 1.8) Relative (%) 1) 4.4 (± 2) 2) 11.3 (± 10) 3) 26.7 (± 18)
1) HA particles mixed with collagen gel and collagen membrane 2) HA particles mixed wtih collagen gel with autologous periodontal ligament stem cells 3) HA particles with collagen gel with BMP-2-expressing autologous periodontal ligament stem cells	(3 mos)	BD – fBIC 1) 80.9 (±2 8.6) 2) 60 (± 34.6) 3) 69.7 (± 12)	Absolute (mm) 1) 0.5 (± 0.4) 2) 0.8 (± 0.7) 3) 2.1 (± 0.7) Relative (%) 1) 12.3 (± 6) 2) 18.8 (± 11) 3) 61 (± 28)
1) No graft 2) Plasma	Nonsubmerged (3 mos)	Achieved (N/A)	Absolute (mm) 1) 0.8 (± 0.4) 2) 1.5 (± 0.5)
No graft	Nonsubmerged (3 mos)	Achieved (N/A)	Absolute (mm) 1) 0.21 (± 0.2) 2) 0.21 (± 0.2) 3) 0.17 (± 0.2) 4) 0.08 (± 0.1)

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Appendix Table 1 *(cont)* **Biofilm Decontamination and Reosseointegration of Titanium Implants: Animal and Human Block Biopsy Studies**

Study	No. of animals, no. and kind of implants, and surface	Peri-implantitis model	Decontamination method
Htet et al[42] (2016)	5 dogs 30 implants anodized surface	Silk ligature (1 mo)	1) Er:YAG laser 2) Diode laser (PDT) 3) Ti bur 4) Ti bur and citric acid
Machtei et al[43] (2016)	5 dogs 30 SA	Retraction cords (2 mos)	24% EDTA
Xu et al[44] (2016)	6 dogs 24 pure Ti	Cotton floss ligature (3 mos)	H_2O_2 (3%) and saline irrigation
Park et al[45] (2017)	4 dogs 16 implants sandblasted with alumina and acid etched	Ligature: 1) Immediately after placement (3 mos) 2) 3 mos after placement (3 mos)	Dental water jet and CHX-soaked floss
Ramos et al[46] (2017)	8 dogs 64 implants SLA	Silk ligatures (3.5 mos)	1) Plastic CURs and cotton pellet soaked with tetracycline 2) Plastic CURs and diode laser (PDT)
Almohandes et al[47] (2019)	6 dogs 48 implants 1) TiO-blasted and acid-etched surface 2) Turned and dual acid-etched surface	Cotton floss ligature (3 mos)	CURs (N/A) and cotton pellets soaked in saline
Morelli et al[48] (2019)	6 dogs 24 TiZr implants: 1) Narrow 2) wide	Ligature (3 mos)	CURs (N/A) and cotton pellets soaked in saline Gauze soaked in saline and irrigation with saline
Sanz-Esporrin et al[49] (2019)	6 dogs 36 TiZr implants SLA	Silk ligature (3 mos)	TiB and Ti CUR and CHX
Viganò et al[50] (2019)	6 dogs 20 TiZr implants Moderately rough	Ligature (3 mos)	1) Sterile saline-soaked gauze 2) TiB

Regenerative therapy groups	Healing type (duration)	Histologic outcomes	
		Reosseointegration (BIC ± SD%)	Vertical bone gain (mm ± SD; fBIC to BD)
Resorbable polylactic membrane	Submerged (3 mos)	5 mm extending from the implant shoulder (%): 1) 13.8 (± 17.2) 2) 2.7 (± 5.8) 3) 8.1 (± 12.1) 4) 22.8 (± 14.5)	N/A
1) β-TCP and collagen membrane 2) β-TCP and endothelial progenitor cells and collagen membrane 3) None	Submerged (3 mos)	4 mm coronal part of the implants (%): 1) 14.6 (± 5.9) 2) 16.7 (± 4.6) 3) 9.3 (± 7.0)	N/A
1) β-TCP 2) β-TCP and adipose-derived stem cells 3) β-TCP with enhanced green fluorescent protein gene transduced 4) β-TCP with BMP-2 gene-modified	Submerged (6 mos)	BD – IS 1) 29.2 (± 2.5) 2) 45.4 (± 3.3) 3) 45.7 (± 3.7) 4) 62.4 (± 4.5)	Absolute (mm) 1) 1.3 (± 0.1) 2) 2 (± 0.1) 3) 2.1 (± 0.2) 4) 2.8 (± 0.2)
HA particles mixed with collagen gel and collagen membrane	Submerged (3 mos)	BD – fBIC 1) 84.6 (± 1 4) 2) 67.4 (± 11.7)	Absolute (mm) 1) 0.7 (± 0.5) 2) 1.8 (± 0.9) Relative (%) 1) 45 (± 18) 2) 17 (± 11)
a) None b) XG and collagen membrane	Nonsubmerged (3 mos)	BD – IS 1a) 36.2 (± 21.9) 2a) 35.5 (± 17.2) 1b) 36.3 (± 21.3) 2b) 27.6 (± 15.3) BD – fBIC 1a) 61.9 (± 21.5) 2a) 61 (± 22.4) 1b) 68.5 (± 22.2) 2b) 59.2 (± 11.8)	Absolute (mm) 1a) 1.0 (± 0.5) 2a) 1.0 (± 0.6) 1b) 1.1 (± 0.5) 2b) 1.2 (± 0.6) Relative (%) 1a) 53 (± 37) 2a) 47 (± 27) 1b) 50 (± 29) 2b) 47 (± 28)
a) None b) XG c) Biphasic bone graft material d) XG and collagen membrane	Nonsubmerged (6 mos)	BD – fBIC 1a) 57.4 (± 9) 1b) 46.7 (± 4.3) 1c) 73.5 (± 11) 1d) 70.9 (± 7.3) 2a) 55.3 (± 10) 2b) 45.2 (± 10) 2c) 45.8 (± 11) 2d) 47.3 (± 13)	Absolute (mm) 1a) 1.2 (± 0.3) 1b) 1.8 (± 0.6) 1c) 1.7 (± 0.3) 1d) 1 (± 0.2) 2a) 1 (± 0.4) 2b) 1.4 (± 0.4) 2c) 1.9 (± 0.8) 2d) 1.4 (± 0.4)
None	Nonsubmerged (5 mos)	N/A	N/A
1) XG and collagen membrane and rhBMP-2 2) XG and collagen membrane	Submerged (2 mos)	BD – IS 1) 40.9 (± 13) 2) 39.5 (± 5.2)	Absolute (mm) 1) 1.01 (± 0.3) 2) 0.9 (± 0.1) Relative (%) 1) 51.1 (± 16) 2) 49.4 (± 7)
None	Nonsubmerged (5 mos)	N/A	N/A

Appendix Table 1 *(cont)* **Biofilm Decontamination and Reosseointegration of Titanium Implants: Animal and Human Block Biopsy Studies**

Study	No. of animals, no. and kind of implants, and surface	Peri-implantitis model	Decontamination method
Yoon et al[51] (2020)	6 dogs 24 implants (N/A)	Silk ligature (1.5 mos)	1) US + 0.5 minocycline hydrochloride with chitosan-alginate microsphere 2) US + placebo 0.5 minocycline hydrochloride with chitosan-alginate microsphere 3) US + 0.5 g minocycline hydrochloride with PG microsphere 4) US (control)
Solderer et al[52] (2021)	12 dogs 48 SLActive	Cotton floss ligature (2 mos)	1) Carbon CUR 2) APA (erythritol) 3) Carbon CUR and APA (erythritol)
Almohandes et al[53] (2022)	6 dogs 48 implants a) TiO-blasted and acid-etched surface b) Turned and dual acid-etched surface	Cotton floss ligature (3 mos)	Saline-soaked cotton pellets and: 1) 40% citric acid gel (30 s) and saline irrigation 2) TiB 3) 40% citric acid gel (30 s) and saline irrigation and TiB 4) None
Human studies			
Wohlfahrt et al[54] (2011)	1 patient 1 implant Rough surface	Peri-implantitis	Ti CUR and 24% EDTA gel (2 min)
Fletcher et al[55] (2017)	1 patient 1 implant Oxide surface	Peri-implantitis	Plastic CUR and cotton pellets soaked in 0.25% NaOCl (1 min) and rinsing with saline and cotton pellet soaked in 1.5% H_2O_2 (1 min)
Kim et al[56] (2018)	1 patient 3 implants SLA	Peri-implantitis	US with copper alloy and cotton balls soaked in solution of saline and 250 mg tetracycline hydrochloride (5 min)
Nevins et al[57] (2020)	3 patients 4 implants (N/A)	Peri-implantitis	Er,Cr:YSGG laser
Bosshardt et al[58] (2022)	3 patients 4 implants 1 HA-coated 3 SLActive	Peri-implantitis	Electrolytic cleaning

APA = air-powder abrasive; BD = bone defect; BIC = bone-to-implant contact; BMP = bone morphogenetic protein; CHX = chlorhexidine; CO2 = carbon dioxide, cpTi = commercially pure titanium; CUR = curette; DFDBA = demineralized freeze-dried bone allograft; ePTFE = expanded polytetrafluoroethylene; Er = erbium; fBIC = first bone-to-implant contact; FDBA = freeze-dried bone allograft; HA = hydroxyapatite; H_2O_2 = hydrogen peroxide; IS = implant shoulder; M = machined; mo(s) = month(s); MTX = microtextured surface; N/A = not available; PDT = photodynamic therapy; PTFE = polytetrafluoroethylene; rhBMP-2 = bone morphogenetic protein 2; rhPDGF = platelet-derived growth factor; s = seconds; SD = standard deviation; SA = sandblasted acid-etched; SLA = sandblasted large-grit acid-etched; SLActive = modified sandblasted large-grit acid-etched; SS = stainless-steel; Ti = titanium; TiB = titanium brush; TiUnite = a slightly negatively charged titanium oxide; TPS = titanium plasma-sprayed; US = ultrasonic scaler; YAG = yttrium-aluminum-garnet; XG = xenograft; β-TCP = beta-tricalcium phosphate.

Regenerative therapy groups	Healing type (duration)	Histologic outcomes	
		Reosseointegration (BIC ± SD%)	Vertical bone gain (mm ± SD; fBIC to BD)
None	Nonsubmerged (2 mos)	N/A	N/A
a) XG bone; collagen membrane b) No bone graft; no membrane	Submerged (2 mos)	Achieved (N/A)	Absolute (mm) 1a) 1.2 (± 0.9) 2a) 2.6 (± 2.4) 3a) 2 (± 0.9) 3b) 1.7 (± 1.0) Relative (%) 1a) 39 (± 34) 2a) 59 (± 44) 3a) 53 (± 17) 3b) 53 (± 29)
None	Nonsubmerged (2 mos)	N/A	N/A
Porous titanium granules	Submerged (6 mos)	achieved (N/A)	N/A
Calcium sulfate + XG + collagen membrane	Submerged (6 mos)	BD – fBIC 37.5%	Absolute (mm) 1.8
Biphasic calcium phosphate bone substitute	Nonsubmerged (6 mos)	Achieved (% as high as the rest of the implant surface)	Distal 1.9 Mesial 1.4
FDBA and cross-linked collagen membrane and rhPDGF	Submerged (6 mos)	Achieved (N/A)	N/A
XG/allograft and collagen membrane	Submerged (6 mos)	BD – fBIC 1) 21% 2) 37% 3) 6% 7) 39%	Absolute (mm) 1) 2.5 2) 3.5 3) 1.3 4) 5.2

Appendix Table 2 Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
Ex vivo studies			
Mouhyi et al[59] (2001) *All references refer to main article reference list.*	9 patients 17 failed implants Machined surface	Ex vivo: failed implants explanted In vitro: treated	1) Ethanol rinse (10 min) 2) Trichloroethylene and ethanol (10 min) 3) APA (sodium bicarbonate; 30 s) 4) Citric acid (30 s) followed by deionized water 5) CO_2 laser in dry condition at 5 W (10 s) 6) CO_2 laser in wet condition at 5 W (10 s)
Hakki et al[60] (2017)	77 failed implants: Zimmer Screw-Vent and SwissPlus	Ex vivo: failed implants explanted In vitro: treated	1) Plastic CUR 2) Ti CUR 3) Carbon CUR 4) TiB 5) Er:YAG laser (100 mJ/pulse at 10 Hz) 6) Er:YAG laser (150 mJ/pulse at 10 Hz) 7) Er:YAG laser (200 mJ/pulse at 10 Hz) 8) US scaler with PEEK 9) APA (glycine) and citric acid (pH 1, 3.4%) 10) Implantoplasty
Rosen et al[61] (2018)	14 failed implants	Ex vivo: failed implants explanted In vitro: treated and evaluated	1) No tx 2) US and hand scaler and cotton pellets with sterile saline 3) US and hand scaler and APA (glycine powder -1 m) and citric acid burnished with cotton pellets
Takagi et al[62] (2018)	4 failed implants with natural calcified deposits	Ex vivo: failed implants explanted In vitro: treated	<u>30 areas cleaned for 40 s:</u> 1) Er:YAG laser 2) Er,Cr:YSGG laser 3) Ti CUR 4) Saline-soaked cotton pellets 5) Control 1 and 2) Spot and sweeping irradiation protocols
Tastepe et al[63] (2018)	13 failed implants SLA	Ex vivo: failed implants explanted In vitro: treated and evaluated	<u>APA tx:</u> 1) HA and BioCaP coating #1 (2.1 mL/min) 2) HA and BioCaP coating #2 (15.2 mL/min) 3) Erythritol and BioCaP coating #1 (2.1 mL/min) 4) Erythritol and BioCaP coating #2 (15.2 mL/min) 5) HA cleaning 6) Erythritol cleaning 7) Cleaning with no powder (control)
Wakim et al[64] (2018)	60 failed implants	Ex vivo: failed implants explanted In vitro: treated	1) Er: YAG laser 50 mJ, frequency of 30 Hz single passage 2) Er:YAG laser 50 mJ, frequency of 30 Hz multiple passages 3) No contamination/no irradiation (negative control)

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM XPS	N/A	1) Organic material on implant surface 2) Small fragment of tissue debris 3) Clean surface with numerous craters, about 10 µm in diameter; number of powder particles attached to the surface 4) Clean surface with nonreflecting spots covering large part of implant surface 5) Burned tissue debris attached to surface 6) Reduced contaminants compared with dry condition	N/A
SEM/EDX	N/A	1) Left plastic remnants 2) Best among manual instruments 3) Left carbon remnants 4) Scratch on the surface 5, 6, 7) Effective in deposit removal, proportional to the intensity, with 7 best in debris removal 8) Failed to clean the surface properly 9) Best results for decontamination 10) N/A	N/A
SEM Cell culture (progenitor osteoblastic cells)	N/A	N/A	Cell cultures (72 h) led to: 1) No growth 2) Few and far between cells 3) Smear layer absent, numerous elongated cells
LM/SEM EDS	SEM: Calculus removal: 1 and 2) Calculus effectively removed 3) Calculus reduced 4) Calculus remained	LM/SEM: Calculus removal: 1 and 2) Microstructures preserved and no melting observed 4) Microstructure preserved 3) Threaded surface damaged to light gray color EDS Ti / C %: 1) 60 / 2.4 2) 54 / 3.6 3) 46 / 4.3 4) 26 / 16 5) 23 / 17.5	N/A
SEM/EDS	SEM/EDS: Pre-tx: Irregularities and mineral accumulations Post-tx: Most large calculus deposits removed, but thin layer left attached to surface of some implants No difference between HA and erythritol powder cleaning regarding this aspect	Some implants showed clusters of powder particles that were attached and covered the surface (less water flow). BioCaP powder particles observed on the Ti surface; SLA structure not damaged and mostly free of biofilm	N/A
SEM EDX	N/A	No presence of any cracks or melted surface in all images; the implant was not affected and the rough surface was similar to that of the sterile implant	N/A

Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
Namour et al[65] (2019)	36 sterile implants 42 failed implants	Ex vivo: failed implants treated In vitro: treated and evaluated	1) Q-Switch Nd:YAG laser (59 mJ/pulse) 2) Temperature test: a) 20 pulses (2 s) 1 mm from lased area b) 20 pulses (2 s) at implant apex c) 40 pulses (4 s) 1 mm from lased area d) 40 pulses (4 s) at implant apex
El Chaar et al[66] (2020)	7 patients Failed implants: SLA anodic oxidized surfaces noncoated microtextured surface	Ex vivo: failed implants, explanted In vitro: treated and evaluated	1) Cotton pellet scrub: 1a) 60 s with saline 1b) 60 s with 0.12% CHX 1c) 60 s with citric acid 40% 1d) 60 s with phosphoric acid gel 35% 1e) 60 s with 3% H_2O_2 2) Implantoplasty 3) APA (sodium bicarbonate) 4) Er:YAG laser (BiolAse - power: 1.5 W; frequency: 30 Hz; air: 40; water: 50) 5) TiB
Tong et al[67] (2020)	30 failed implants SLA	Ex vivo: failed implants, explanted In vitro: treated and evaluated	One side of implant was not cleaned (control) Other side of implant was treated with: 1) Saline irrigation 2) APA (glycine) 3) APA (glycine) and EDTA with interdental brush 4) PEEK US scaling and saline 5) PEEK scaling and EDTA
Linden et al[68] (2021)	5 patients 6 failed implants	Ex vivo: failed implants treated in vivo and then explanted In vitro: evaluated	1) US tip and CHX and Nd:YAG laser 2) Er,Cr:YSGG laser 3) Er:YAG laser 4) CO_2 laser 9,300 nm (2 implants) 5) CO_2 laser 10,600 nm
Pranno et al[69] (2021)	20 patients > 4 failed implants	Ex vivo: failed implants treated in vivo and explanted In vitro: evaluated	1) APA (sodium bicarbonate and glycine) 2) Cotton pellets soaked in 3% H_2O_2 and 0.2% CHX 3) Combination of 1 and 2 4) No tx

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM EDS Temperature	SEM: 1) Nd:YAG laser with short pulse duration in nanoseconds able to sig clean contaminated implant surfaces	Utilized parameters did not alter surfaces	N/A
SEM	Implant Debridement Visual Index: tx 1a, 1b, 1c, 1d, 1e) No removal tx 3, 4, 5) Some removal tx 2) Complete removal	N/A	N/A
SEM: a) RCAR b) VAS c) Surface roughness EDS	SEM: 1) No difference to control 2, 3, 4, 5) Reduced contaminants in neck and thread areas vs 1 Reduction in contaminated area: 1) 33% 2) 67% 3) 61% 4) 83% 5) 83% VAS by examiner: tx 4) Seemed to present significant improvement	Surface roughness: No sig difference in any group SEM: PEEK remnants in tx 4 and tx 5 Surface chemistry: tx 2, tx 3, tx 4, and tx 5: C%, O% decreased; Ti% increased tx 3) O% decreased; Ti% increased	N/A
SEM	1) Complete decontamination 2) Complete decontamination 3) No bacteria evident 4) Random dispersed aggregates of bacteria 5) Complete decontamination	1) No evidence of heat-induced surface damage; residual bone adhering to implant surface displayed honeycomb-like etched surface 2) Small areas of localized surface damage; visible porous globules indicating melting and bone HA mineral resolidification 3) Clotted blood, fibrin, collagen fibers, some areas of attachment 4) Areas of adherent fibrous connective tissue; residual bone exhibited honeycomb-like appearance consistent in texture with etching effect 5) N/A	N/A
CFU	Log10 CFU/mL 1) 5×10^2 2) 3×10^4 3) 9×10^2 4) 4×10^4	N/A	N/A

Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
Secgin-Atar et al[70] (2021)	28 implants	Ex vivo: failed implants and explanted In vitro: treated and evaluated	1) Ti CUR 2) US scaler with PEEK tip 3) Er:YAG laser 120 mJ; pulse duration: 3a) 100 µs 3b) 300 µs 3c) 600 µs 4) Er,Cr:YSGG laser, pulse energy: 4a) 100 mJ 4b) 50 mJ 5) Sterile implant
La Monaca et al[71] (2022)	20 patients > 3 failed implants	Ex vivo: failed implants treated in vivo and explanted In vitro: evaluated	1) APA (sodium bicarbonate) 2) APA (sodium bicarbonate) and amino acid–buffered hypochlorite solution 3) No tx (control)
Qian et al[72] (2022)	26 patients 30 implants TiUnite SLA	Ex vivo: failed implants explanted In vitro: treated and evaluated	1) Saline irrigation 2) APA (erythritol) 3) APA (erythritol) and EDTA with interdental brush 4) US scaling with PEEK 5) US scaling with PEEK and EDTA with interdental brush 6) US scaling with PEEK and APA (erythritol) and EDTA with interdental brush
Wawrzyk et al[73] (2022)	2 patients 2 failed implants	Ex vivo: failed implants treated in vivo and explanted In vitro: evaluated	Diode laser 25 W/15,000 Hz/10 µsl 1) Unirradiated 2) 2 times at 15 s 3) 3 times at 15 s
Bernardi et al[74] (2023)	2 patients 3 failed implants	Ex vivo: failed implants explanted In vitro: treated and evaluated	Electric field: 4 cycles of 3 s unipolar
Ichioka et al[75] (2023)	25 patients 34 failed implants a) Oxide b) TiO_2-blasted c) TiO_2-blasted fluoride-modified d) Grit blasted and acid etched e) SLA	Ex vivo: failed implants explanted In vitro: treated and evaluated	1) APA (erythritol) wiped with NaCl 0.9% soaked gauze (surface a, c, d) 2) APA (erythritol) wiped with gauze soaked in alkaline-electrolyzed water 0.1% (surface a, b, c, e) 3) No tx (surface a, c, e)

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM EDS Profilometry	SEM: Implant debridement visual index: tx 3c) Most effective, followed by tx 2 "debris not removed" score greater for tx 1, tx 4	SEM: 1) Large and flat scratched areas 2) Remnants of PEEK 3a) Delamination and deformation, surface with microcracks 3b) Delamination, deformation, and melting 3c) No damage 4a) No damage, debris remains 4b) Debris remains EDS: Lowest C% detected in tx 5 and tx 3), tx 4 after debridement	N/A
CFU Microbial ID	Log_{10} CFU/mL 1) 6×10^4 2) 3×10^2 3) 9×10^4 Neisseria subflava most prominent in biofilm	N/A	N/A
CAR (SEM/SM) VAS Light interfero-metry EDS	SEM/SM: Reduction of contaminants after debridement: 1) 30% / 17% 2) 56% / 77% 3) 67% / 79% 4) 75% / –154% 5) 66% / –184% 6) 90% / 84%	SEM 4 and 5) Negative reduction (increase) due to PEEK remnants 6) Less roughness after tx, produced almost maximum C% decrease and Ti% increase	N/A
Optical microscopy Optical profilometers	CFU/mL regarding gram-negative, gram-positive bacteria and fungi reduced sig (> 95) from 1 to 2 or 1 to 3	Diode laser does not deteriorate surface roughness of Ti implants	N/A
SEM	SEM: Absence of biofilm in observed area	N/A	N/A
SEM EDS Cellular proliferation and adhesion	SEM: Areas of residual bacteria 1) 629 (± 958) µm2 (7%) 2) 325 (± 310) µm2 (4%) Areas of mineralized deposits: 1) 981 (± 813) µm2 (12%) 2) 529 (± 790) µm2 (6%) Residual biofilm by surface type: a) At gaps between crystals b) Bacteria in porous structures c) Between micropits	SEM: No residual powder-like deposits evident on any evaluated surfaces; gauze deposits rarely detected at applied magnification EDS – %C: 1) 7.3% 2) 5% 3) 70%	N/A

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Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
In situ studies			
Augthun et al[76] (1998)	4 patients 8 implants a) Plasma-sprayed surface b) Smooth surface	In situ: oral biofilm developed on implants (7d) In vitro: treated and evaluated	60 s 1) CHX 0.1% rinse 2) Plastic CUR 3) APA (sodium bicarbonate)
Schwarz et al[77] (2006)	3 volunteers 30 discs SLA	In situ: oral biofilm developed on discs (24 h) In vitro: treated and evaluated	Er,Cr:YSGG laser 0.5, 1.0, 1.5, 2.0, and 2.5 W using 25 Hz
Schwarz et al[78] (2006)	5 volunteers 30 discs SLA	In situ: oral biofilm developed on discs (72 h) In vitro: treated and evaluated	1) US system with PEEK and CHX 2) Plastic CUR and CHX
Schwarz et al[79] (2009)	6 patients 160 discs	In situ: oral biofilm developed on discs (48 h) In vitro: treated and evaluated	1) APA (glycine) 2) APA (sodium bicarbonate) 3) No tx, noncontaminated
Gosau et al[80] (2010)	14 patients 56 Ti discs machined	In situ: oral biofilm developed on discs (12 h) In vitro: treated and evaluated	Discs covered 1 min with: 1) NaOCl 2) 3% H_2O_2 3) 0.2% CHX 4) Triclosan (Plax) 5) Essential oils (Listerine) 6) 40% citric acid
Tastepe et al[81] (2013)	14 patients 36 discs SLA	In situ: oral biofilm developed on discs (48 h) In vitro: treated and evaluated	1) APA without powder (water and air pressure) (control) 2) Mechanical APA tx: 2a) HA 2b) HA and TCP 2c) TiO_2 2d) Glycine 3) Phosphoric acid (chemical)
Idlibi et al[82] (2013)	5 humans 20 discs machined	In situ: oral biofilm developed on discs (48 h) In vitro: treated and evaluated In situ: oral biofilm developed on discs (72 h) In vitro: treated and evaluated	1) Gas control 2) Cold atmospheric plasma 3) Diode laser 4) APA (glycine) 5) CHX (submerged)

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM	SEM: 1) Did not remove plaque deposits on surfaces 2) Did not remove plaque in depths of screw-type threads or on plasma-sprayed surfaces 3) Completely plaque-free surface on all fixtures	SEM (sterile implants): Plasma-sprayed surface 1) No damage 2 and 3) Minimal damage Smooth titanium 1, 2, 3) No damage	SEM: 2) Cell number sig reduced 3) Most vital cells
SEM LM (cell viability – Saos-2 osteoblasts)	Mean residual plaque areas decreased significantly with increasing energy settings (53.8 – 2.2 at 0.5 W to 9.8 – 6.2 at 2.5 W)	SEM: No signs of any laser-induced thermal side effects	LM: 2.5 W (25 Hz) – sig lowest mitochondrial activity of Saos-2 osteoblasts
SEM LM (Saos-2 osteoblasts)	Residual plaque area: 1) 28% to 38% 2) 58% Remarkable amounts of residual plaque areas noted in microrelief in Ti surfaces in both groups, especially 2	N/A	LM: Low mitochondrial activity of Saos-2 osteoblasts
SEM LM (Saos-2 osteoblasts)	Residual plaque area: Range: 0% to 6%; no difference between groups	No powder deposition on surface of any group	LM: Mitochondrial activity of Saos-2 cells highest in tx 3 followed by tx 2, exhibiting sig greater mean values than tx 1
Cell viability (live/dead), Fluorescence microscopy	Dead/total cells ratio (%) 1) 74% 2) 65% 3) 68% 4) 30% 5) 77% 6) 59%	N/A	N/A
SEM LM EDS	LM: tx 2b, 2c, 2d) Decreased biofilm amount better than tx 1 (control)	SEM: 2a–2d) All APA groups led to rounded edges around the grooves and showed residual powder particles 2a and 2b) Surface structure similar 2c) Minimal change EDS: Bioactive powder particles left attached to surface	N/A
Fluorescence Microscopy culture	Residual biofilm: 1) 91.8% 2) 28%–60% 3) 38% 4) 2.5% 5) 71% 6) 68%	N/A	N/A

Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
John et al[83] (2014)	6 patients 60 discs SLA	In situ: oral biofilm developed on discs (48 h) In vitro: treated and evaluated	1) Steel CUR 2) TiB 3) No tx on unworn discs
Charalampakis et al[84] (2014)	20 patients 80 discs a) Blasted and acid-etched surface b) TiOblast c) Experimental d) Turned	In situ: oral biofilm developed on discs (4 d) In vitro: treated and evaluated	Discs cleaned for 5 s, using 3 strokes with cotton pellet soaked in: 1) NaCl 2) CHX 3) Decapinol 4) Essential oils (Listerine)
Al-Hashedi et al[85] (2016)	6 patients Ti discs (N/A)	In situ: oral biofilm developed on discs (24 h) In vitro: treated and evaluated	1) Electrochemical (+1.8 V; 2.5 min and –1.8 V; 2.5 min) 2) TiB 2) Electrochemical and TiB
Al-Hashedi et al[86] (2017)	4 patients 48 discs machined	In situ: oral biofilm developed on discs (24 h) In vitro: treated and evaluated	1) Stainless steel CUR 2) Plastic CUR 3) TiB 4) Er:YAG laser
John et al[87] (2016)	5 patients 138 discs a) Ti sandblasted large-grit and acid-etched discs b) Zr discs	In situ: oral biofilm developed on discs (48 h) In vitro: treated and evaluated	1) APA (sodium bicarbonate) 2) APA (gylicine) 3) APA (glycine and TCP) 4) No tx (unworn discs)

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM Cell culture Time to clean	Residual plaque area (%): 1) 29 (± 5.5) 2) 8.6 (±4.9) Time to clean (s): 1) 303.5 (±11.5) 2) 176.7 (± 15)	N/A SEM: 1) Sig alterations, like leveling of typical sharp peaks in SLA surface 2) No surface alteration	1 vs 2) No sig difference in cell viability 1) Day 3: 14,644 (± 11,938.44) CPS; day 6: 8,440.8 (± 8,607.4) CPS 2) Day 3: 744 (± 642.1) CPS; day 6: 836 (± 416.75) CPS 3) (control) Day 3: 83,552 (± 5,642.37) CPS; day 6: 179,542 (± 37128.46) CPS
SEM (visual analysis) CFU	SEM: d) Thin bacterial layer a, b, c, e) Surfaces: much thicker bacterial layer vs d CFU: No sig differences between surface types or between tx groups 1–4	N/A	N/A
SEM XPS	SEM 1) Removed bacteria and other surface contaminants with minimal surface changes; sig reduction in no. of attached bacteria and viability 2) Not sufficient to remove biofilm 3) Sig drop in the no. of attached bacteria and viability	SEM 2 and 3) TiB induced a change in Ti surface morphology and roughness XPS 3) Concentrations of all surface elements similar to clean Ti	N/A
SEM XPS Fluorescence microscopy	Fluorescence microscopy: tx 1 and tx 3) Almost as clean as uncontaminated surfaces tx 4) No change in number of bacteria; more dead bacteria covering all surface	SEM: 1) Obvious morphology changes; pronounced scratch lines 2) Pronounced scratch lines 3) Surfaces free of scratches 4) Surfaces free of scratches but with residual bacteria XPS: 1, 2, and 3) Sig increased oxygen levels 2 and 3) Sig increased Ti levels compared to contaminated surfaces 3) Reduced nitrogen levels 4) Lowest surface changes in favor of decontamination	N/A
SEM Cell culture	SEM: Residual plaque: Ti: tx 1 (1.51 ± 1.40 %) > 2 (0.44 ± 0.69 %) > 3 (0.10 ± 0.26 %). Zr: tx 2 (0.24 ± 0.71 %) > 1 (0.14 ± 0.26 %) > 3 (0.01 ± 0.03 %) All surfaces showed completely clean areas; no remnants of biofilm	SEM: Ti discs Only scarce surface alterations, eg, minimal flattening of sharp surface edges; minimal % powder remnants Zr discs: No surface alterations; remnants of the different powders	Saos-2 culture: Ti discs: No difference between tx groups Zr discs: tx 1, 3, 4) Comparable cell viability on day 6

Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
Alotaibi et al[83] (2018)	6 patients 24 implants attached to complete denture a) Anodized surface b) Dual acid-etched surface	In situ: oral biofilm developed on discs (30 d) In vitro: treated and evaluated	TiB and cotton pellet with 3% H2O2 (1 min)
Koch et al[89] (2020)	6 patients 24 Ti-Zr discs Rough Smooth	In situ: oral biofilm developed on discs (24 h) In vitro: treated and evaluated	1) No tx (control) 2) CUR and CHX (chemical-mechanical) 3) Boron-doped DDE 2.5 min (electrical) 4) Boron-doped DDE 5 min (electrical)
Otsuki et al[90] (2020)	11 patients 6 implants on intraoral splint a) Rough b) Machined	In situ: biofilm developed on implants (4 d) In vitro: implants treated and evaluated	1) Saline-soaked gauze 2) US scaler 3) APA (glycine) 4) Stainless steel rotatory brush 5) Er:YAG laser 60 mJ/pulse 6) No tx, not contaminated (control)

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM CFU Bacterial ID	Bacterial ID: Streptococci predominant bacteria Log_{10} CFU/mL: a) 7×10^2 b) 5×10^2	SEM: Flat surfaces or partially disfigured topography	N/A
CFU Mass spectrometry	2) Not effective in microbe removal 3 and 4) Reduced growth; higher potential had a positive effect	N/A	N/A
SEM CFU	SEM: tx 1, 3, 4) > 2 cleansability Cleansability: a) Rough: 1 and 4) Good on micro- and macrothreads 2 and 3) Good on macrothreads 5) No cleansability on micro- or macrothreads b) Machined: 1 and 4) Excellent on micro- and macrothreads 2 and 3) Good on micro- and macrothreads 5) Fair to good on micro-/ macrothreads All tx groups: b > a surfaces SEM: tx 1, 3, 4) > 2 cleansability Cleansability: a) Rough: 1 and 4) Good on micro- and macrothreads 2 and 3) Good on macrothreads 5) No cleansability on micro- or macrothreads b) Machined: 1 and 4) Excellent on micro- and macrothreads 2 and 3) Good on micro- and macrothreads 5) Fair to good on micro-/ macrothreads All tx groups: b > a surfaces Log_{10} CFU/mL a) Rough: 1) 10^5 2) 10^6 3) 10^6 4) 10^5 5) 10^6 6) 10^7 b) Machined: 1) 10^4 2) 10^6 3) 10^5 4) 10^5 5) 10^6 6) 10^7	N/A	N/A

Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
Park et al[91] (2020)	6 patients 48 Ti discs	In situ: oral biofilm developed on discs (72 h) In vitro: treated and evaluated	1) Er:YAG laser 2) Er,Cr:YSGG laser 3) Plastic CUR 4) No tx (control)
AlMoharib et al[92] (2021)	8 patients 59 discs SLA	In situ: oral biofilm developed on discs (72 h) In vitro: treated and evaluated	1) Er:YAG laser (80 mJ/pulse) 2) TiB 3) Carbon fiber CUR 4) No tx (control)
Huang et al[93] (2021)	10 patients 40 discs SLA HA	In situ: oral biofilm developed on discs (72 h) In vitro: treated and evaluated	1) Er:YAG laser: 1a) 40 mJ/pulse 1b) 70 mJ/pulse 1c) 100 mJ/pulse 2) No tx (unworn/clean; blank control) 3) No tx (worn intraorally, contaminated)
Birang et al[94] (2022)	10 patients 7 Ti discs SLA	In situ: oral biofilm developed on discs (24 h) In vitro: treated and evaluated	1 min exposure to: 1) Er:YAG laser 2) Cotton pellet and saline 3) Plastic CUR 4) APA (glycine) 5) Plastic CUR and cotton pellet with 3% H_2O_2 6) Plastic CUR and diode laser 980 nm
Lollobrigida et al[95] (2022)	3 patients 96 discs SLA machined	In situ: oral biofilm developed on discs (24 h) In vitro: treated and evaluated	1) TiB (20 s) 2) TiB and 5.25% NaOCl 3) TiB and 40% liquid citric acid 4) APA (glycine) (20 s) 5) APA (glycine) and 5.25% NaOCl 6) APA and 40% citric acid 7) Control

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
SEM Fluorescence microscopy	SEM: Residual plaque area (%): 1) 10.3 (± 2.4) 2) 7.0 (± 2.5) 3) 12.3 (± 3.6) Fluorescence microscopy: 1 and 2) (1.7% and 1.5%) less total live and dead bacteria vs 3 (4.9%) 2) Sig less viable bacteria vs 3 after tx (0.3% and 2.4%)	N/A	N/A
Fluorescence microscopy	Residual biofilm (%): 1) 74 (± 22) 2) 33 (± 24) 3) 12 (± 10) 4) 20 (± 19)	N/A	N/A
SEM Fluorescence microscopy CFU Cell counter kit 5: cell viability (mouse calvarial osteoblastic cells)	Removal of bacteria (%): SLA: 1a) 40 – 38 1b) 70 – 63 1c) 100 – 84 HA: 1a) 40 – 59 1b) 70 – 76 1c) 78 – 100	Laser scavenging effect increased with increasing laser energy SLA: Morphologic changes following melt and ridges decreased or even disappeared (> high laser energy) HA: 1b) Remarkable surface melting 1c) Surface coating almost completely peeled off or cracked, leaving rough surface Wettability after tx 1a–1c: SLA: Contact angles decreased, no difference between settings or to tx 2	Greater cellular proliferation activity than tx 2 at 7 d HA: Less cellular proliferation activity than tx 2 at 7 d
CFU	1) Most effective on bacterial count reduction (both aerobic and anaerobic) 2 and 3) Least effective	N/A	N/A
SEM XPS Cell culture (human osteoblasts) CFU	SEM: SLA: 1, 2, 3) Left large amounts of organic debris and residual bacteria, isolated or in clusters 4, 5, 6) Little organic debris Machined: 1, 2, 3) Left little organic debris; 4, 5, 6) Left no debris; NaOCl dissolved residual bacterial cells to a greater extent than citric acid CFU: 1–6) Effective against biofilm as compared to tx 7 2, 3, 5, 6) (mechanical and chemical) Sig more effective than tx 1, tx 4 (mechanical) TiB (tx 1, 2, 3) More effective on machined vs SLA surfaces	XPS: Ti on all tx disks, discs with NaOCl most, citric acid least 1, 2, 3 [TiB tx]): Sig alterations of surface microtopography 4, 5, 6 [APA]): No changes observed after	At 14 d, osteocalcin release by human primary osteoblasts was greater on SLA in tx 1, tx 4, and machined tx 2 through 6, reduced in SLA tx 5, tx 6, and machined tx 1; hOBs cells had lower proliferation rate on SLA in tx 2, tx 5 (NaOCl) vs SLA tx 1, tx 4 (no chemical) 6) Scarce, poor adhesion

Appendix Table 2 *(cont)* **Biofilm Decontamination of Implants and Disc Surfaces: Ex Vivo and In Situ Studies**

Study	No. of patients, no. and type of implants/discs, type of surface	Experimental model	Decontamination method
Kottman et al[96] (2023)	1 patient 92 machined Ti discs	In situ: oral biofilm developed on discs (16 h) In vitro: treated and evaluated	1) APA (glycine) (20 s) 2) Er,Cr:YSGG laser (1.5 W; 30 Hz) (60 s) 3) Er,Cr:YSGG laser (0 W) (60 s) 4) No tx (control)
Wang et al[97] (2023)	8 patients 64 discs	In situ: oral biofilm developed on discs (72 h) In vitro: treated and evaluated	1) CHX and PDT 2) CHX and Er:YAG laser 3) CHX 4) No tx (control)

APA = air-powder abrasive; BioCaP = biomimetic calcium phosphate; C% = percentage (proportion) of carbon; CAP = cold atmospheric plasma;
CFU: colony-forming units; CP = cotton pellets; CO2 = carbon dioxide (laser); CUR = curette; d = day; DDE = double-diamond electrode; EC = experimental control;
EDS = energy dispersive spectroscopy; Er,Cr:YSGG = erbium, chromium: yttrium-scandium-gallium-garnet (laser); Er:YAG = erbium: yttrium-aluminum-garnet (laser);
GE = genome equivalent; h = hour; HA = hydroxylapatite; H_2O_2 = hydrogen peroxide; hOBs = human osteoblasts; LM = light microscopy; min = minute;
N/A = not applicable or not available; NaOCl = sodium hypochlorite; Nd:YAG = neodymium-doped yttrium-aluminum-garnet (laser);
O% = percentage (proportion) of oxygen; PEEK = polyetheretherketone; RCAR = relative contaminated area reduction; s = second;
Saos-2 = "sarcoma osteogenic" cell line; SEM = scanning electron microscopy; sig = significant(ly); SA = sandblasted acid-etched;
SLA = sandblasted large-grit acid-etched; TCP = tricalcium phosphate; Ti = titanium; Ti% = percentage (proportion) of titanium; Ti-Zr = titanium-zirconium;
TiB = titanium brush; TiO2 = titanium dioxide; TiUnite = a slightly negatively charged titanium oxide; tx = treatment (group); US = ultrasonic scaler;
VAS = visual analog scale; W = watts; XPS = x-ray photoelectron spectroscopy; Zr = zirconia.

Evaluation technique	Residual bacteria/ deposits	Alterations on the surface	Cell culture
qPCR (GE)	GE values: 1, 2, 3) Sig reduced compared to 4 but with no sig differences among them	N/A	N/A
Confocal laser scanning microscopy	Residual vital biofilm: 1) 43.9% 2) 32.2% 3) 56% 4) 73.2% Residual dead biofilm: 1) 56.6% 2) 67.3% 3) 43.4% 4) 7.9%	N/A	N/A

Appendix Table 3 Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Marotti et al[98] (2013)	60 implants TiUnite anodized with rough surface	Saliva from 1 volunteer with peri-implantitis Implants kept in saliva (5 min)	1) Contaminated and not decontaminated (negative control) 2) Immersed in 0.12% CHX (5 min) (positive control) 3) PDT (laser and dye) (3 min) 4) PDT (laser and dye) (5 min) 5) PDT (laser; no dye) (3 min) 6) PDT (laser; no dye) (5 min)	CFU
Duske et al[99] (2015)	80 Ti discs SLA	Plaque samples from 1 volunteer with periodontitis discs incubated in medium (plaque and DMEM) at 37°C (7 d)	1) Nylon brush 2) Plasma (argon and 1% O_2) 3) Combination of 1 and 2 4) Contaminated and not decontaminated (negative control) 5) Noncontaminated (positive control) 6) Autoclaved biofilm (positive control)	SEM cell culture (human osteoblasts
Kotsakis et al[100] (2016)	24 Ti discs Grit-blasted acid-etched	Plaque samples from 1 volunteer with peri-implantitis Discs incubated in medium (microcosm) in anaerobic conditions at 37°C (48 h)	Discs burnished for 20 s with cotton pellets moistened in: 1) 0.12% CHX 2) 20% citric acid gel 3) 24% EDTA/1.5% NaOCl 4) 0.9% sterile saline NaOCl 5) Noncontaminated (control)	CFU XPS Wettability assay Cell culture (murine osteoblasts)
Eick et al[101] (2017)	Ti discs (N/A) SLA Pocket model	Discs incubated in suspension of polymicrobial biofilm (12 strains) (120 h)	1) Ti CUR (20 strokes) 2) Er:YAG laser [50 mJ (on panel)-20 Hz/pulse] 3) PDT 4) Ti CUR (10 strokes) and PDT 5) Untreated contaminated control 6) Noncontaminated control	CFU cell culture (epithelial cells, human fibroblasts, and human osteoblasts)
Giannelli et al[102] (2017)	42 Ti discs Rough TiO_2	Plaque samples from 6 patients with peri-implantitis smeared on surface of discs discs fixed in 95% ethanol to simulate hardened plaque, dried and kept at 4°C	1) US piezo scaler (1 min) 2) Er:YAG laser (20.3 J/cm^2 (1 min) 3) Er:YAG laser (38.2 J/cm^2 (1 min) 4) Untreated contaminated control 5) Noncontaminated control	SEM: live/dead stain Cell culture (human osteoblasts) Confocal LSM
Matthes et al[103] (2017)	42 Ti discs SA	Plaque samples from 1 volunteer with periodontitis Discs incubated in medium with plaque (7 d)	1) APA (erythritol) (90 s) 2) Argon CAP in liquid medium (300 s) 3) Argon CAP in liquid medium (720 s) 4) APA and CAP (300 s) 5) APA and CAP (720 s) 6) Contaminated (negative control) 7) Noncontaminated (positive control)	SEM Cell culture (osteosarcoma cells) Wettability

All references refer to main article reference list.

Residual bacteria/deposits	Surface alterations	Cell culture
Log_{10} CFU/mL: 1) 5×10^5 2) 6×10^2 3) 2×10^3 4) 6×10^2 5) 1×10^4 6) 1×10^4	N/A	N/A
SEM 1) Original disc topography observed 2) Remnants of biofilm obscured original disc structure 3) Original disc topography observed 4) Biofilm completely covered and obscured disc topography 5) N/A 6) Amorphous layer of dead biofilm covered disc topography	N/A	SEM cell culture (5 d): Dense layer of cells only occurred in 3, 5
Antimicrobial effect: 2 and 3) Most reduced CFU counts, followed by 1 4) Minimal efficacy	XPS: 1) Increased C% 3) Increased C%, highest O% 4) Increased C% Wettability: 1–4) Increased wettability vs 5 (control) 3) Highest wettability (reduced contact angles, 16.5 ± 6.2)	All tx surfaces had some cytotoxic effect, no. of cells sig reduced vs controls 4) Larger no. of cells 1) Smallest no. of cells
Residual Log_{10} CFU/mL: 51) 10^4 2) 10^2 3) 10^4 4) 10^3 5) 10^6 6) N/A	N/A	Epithelial cells: No. increased sig after any tx, except 4 Cell adherence higher to surface without biofilm 6 Fibroblasts: 2) Sig cell count increase Osteoblasts: 2) Sig cell count increase
SEM: Residual plaque (%) 1) 11.7 ± 2.3 2) 32.2 ± 8.2 3) 0.03 ± 0.001 4) 76.5 ± 2.1 5) N/A	SEM: 1) Markedly flattened surface with scraping grooves and disappearance of microcavities; incomplete removal of TiO_2 layer; scanty aggregates of plaque-like material 2) Little residual plaque; large remnants of surface TiO_2 layer between areas of clean, micropitted Ti surface 3) Both plaque and TiO_2 layer completely stripped away, leaving micropitted Ti surface; no signs of melting or other heat-induced deformation	1 and 3 similar to 4) Surface changes did not substantially compromise osteoblastic cell growth, adhesion, and viability 2) Left too much bacterial plaque to allow Saos-2 cell attachment and culture
SEM: Bacteria count (5 d) (%): 1) 0 2) 96.8 ± 2.9 3) 94.6 ± 13.3 4) 0 5) 0 6) 94.9 ± 6.9 7) 0	Wettability: water contact angle (degrees): 1) 4.3 ± 4.1 2) 7.1 ± 2.3 3) 6.6 ± 0.9 4) 0 5) 0	Cell count (5 d) (%): 1) 84.7 ± 16.5 2) 0 3) 1 ± 7.3 4) 75.2 ± 18.1 5) 57.5 ± 18.7 6) 0 7) 77.7 ± 21.2

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Appendix Table 3 *(cont)* **Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies**

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Tastepe et al[104] (2018)	96 Ti discs Ca-precipitated, organic film layer–coated SA	Discs incubated in medium with saliva from 1 volunteer with healthy periodontium (96 h)	1) APA (96% erythritol and 4% HA) and BioCaP coating (4% BioCaP and 96% erythritol): 1a) High water flow 1b) Low water flow 2) APA (erythritol) and BioCaP coating (4% BioCaP and 96% erythritol): 2a) High water flow 2b) Low water flow 3) APA (erythritol and HA) 4) APA (erythritol) 5) Contaminated (negative control) 6) Noncontaminated (positive control)	SEM Cell culture (osteoblast-like cells) Cell attachment, cell viability, and proliferation
Han et al[105] (2019)	Ti discs SA	Discs incubated in medium with saliva from 1 volunteer in anaerobic conditions at 37°C (48 h)	1) 40% citric acid (1 min) 2) 40% citric acid (5 min) 3) 0.4% CHX (5 min) 4) 0.8% CHX (5 min) 5) 6% H_2O_2 (1 min) 6) 12% H_2O_2 (1 min) 7) Distilled water (control)	CFU (at day 3)
Jin et al[106] (2019)	68 Ti discs SA	Discs incubated in medium with saliva from 1 volunteer with healthy periodontium in anaerobic conditions (48 h)	<u>US devices:</u> 1) US metallic tip 1 2) US metallic tip 2 3) US plastic tip 1 (PEEK) 4) US plastic tip 2 5) US Ti tip <u>Rotating instruments (40 s):</u> 6) Stainless steel brush 7) Ti brush 8) Nylon brush 9) APA (glycine) (10 s) 10) Er,Cr:YSGG laser (40 s) <u>Chemical decontamination (20 strokes, cotton pellets):</u> 11) 3% H_2O_2 12) 50% citric acid 13) 24% EDTA 14) Tetracycline 15) No tx, pellicle with biofilm 16) No contamination, only pellicle coating 17) Sterilized disc (control)	SEM Cell culture (human osteoblast) EDS
Ratka et al[107] (2019)	72 implants Ti grade 4 or 5 a) SA b) Anodic oxidation	Implants incubated in medium with saliva from 3 volunteers with healthy periodontium at 37°C (14 d)	1) Electrolytic cleaning (6 V, 1,100 mA) 2) APA (glycine) (60 s)	CFU
Koch et al[108] (2020)	45 implants SLA placed in bovine ribs	Implants inoculated with 8-species medium to create biofilm at 37°C (3 d)	1) Stainless steel CUR and CHX 0.2% 2) APA (erythritol) and CHX 0.2% 3) Electrochemical cleaning: boron-doped diamond (0, 5, 10, and 15 min)	CFU (implants were rolled on blood agar plates)

Residual bacteria/deposits	Surface alterations	Cell culture
N/A	N/A	Cell viability (2 d): 1a, 1b, 3) 4 times higher than 6 2a and 2b) 5 times higher than 6 4) 6 times higher than 6 Cell viability (4 d): 2a, 2b, 4): Higher cell viability vs 1a, 1b, 3; coating step only showed minimal influence Cell viability (6 d): Cleaning step did not have sig influence vs 4 d; BioCaP coating step caused sig difference vs no BioCaP coating
Residual Log_{10} CFU/biofilm: 1) 10^5 2) 10^6 3) 10^5 4) 10^5 5) 10^6 6) 10^5 7) 10^8 Biofilm composition in 7 was sig different from 6 and from other tx groups	N/A	N/A
N/A	EDS: 17) only Ti% on surface O% most abundant on instrumented surfaces C% detected in most instrumented groups, except metal- and Ti-instrumented groups	Cell proliferation (2 d): 7, 8, 10) Sig higher vs 17 Cell proliferation (5 d): Sig lower in all decontaminated discs, except for 3 and 4 7) Cell density lower All tx groups showed well-attached cells Cytocompatibility: No decontamination, tx similar to 17
1a) No CFU could be counted 1b) No CFU could be counted 2a) > 200 CFUs 2b) > 200 CFUs	N/A	N/A
CFU 3) At 10 or 15 min > 2 and 1, but disinfection incomplete	N/A	N/A

Appendix Table 3 *(cont)* **Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies**

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Namour et al[109] (2020)	52 discs SLA	Discs incubated in medium with 14-species community in microaerophilic conditions (48 h)	1) Q-Switch Nd:YAG laser (270 mW) (2 s) 2) Contaminated, no tx 3) Sterile, irradiated 4) Sterile, no tx	SEM (crystal violet assay)
Amate-Fernandez et al[110] (2021)	52 implants (N/A) Artificial mouth	Implants incubated in medium with 6-species biofilm in anaerobic conditions at 37°C and pH = 7.2 (14 d)	1) APA (erythritol) 2) Gauze with sterile saline 3) Negative control	SEM qPCR Regrowth (7 d)
Cordeiro et al[7] (2021)	20 Ti discs Machined SLA	Discs incubated in saliva from 3 healthy volunteers in medium at 37°C (72 h)	1) 10% citric acid (1 min) 2) 10% citric acid (2 min) 3) 10% citric acid (4 min) 4) 10% citric acid (8 min)	SEM and CFU
Hui et al[111] (2021)	35 pure Ti implants Moderately rough surface blasted with alumina particles	Implants incubated in medium with saliva from 1 volunteer with peri-implantitis in anaerobic conditions at 37°C (96 h)	1) APA (erythritol) (80s) 2) CAP 3) APA and CAP 4) Incubated without human saliva (negative control) 5) Noncontaminated (positive control)	SEM (crystal violet assay)
Hui et al[112] (2021)	112 Ti discs a) Machined b) Rough alumina particles-blasted	Discs incubated in medium with saliva from 1 volunteer with peri-implantitis in anaerobic conditions at 37°C (96 h)	1) APA (erythritol) (20 s) 2) CAP 3) APA and CAP 4) Noncontaminated and treated with APA and CAP (negative control) 5) Contaminated and untreated (positive control)	SEM Crystal violet assay LCPM
Kotsakis et al[113] (2021)	200 Ti discs Acid-etched Microrough	Discs incubated in medium with plaque samples from 1 volunteer with peri-implantitis in anaerobic conditions at 37°C (48 h)	Discs cleaned (30 s) with: 1) Rotary nylon brush 2) Ti brush 3) Water jet with high pressure 4) Water jet with low pressure 5) Sterile saline (untreated control) 6) Immersion in 0.12% CHX (positive control)	SEM CFU Atomic force microscopy (AFM) Corrosion resistance (OCP) ICP-MS Cell culture (murine osteoblasts and fibroblasts): proliferation and differentiation

Residual bacteria/deposits	Surface alterations	Cell culture
SEM: 1) 0.004 ± 0.004 2) 0.120 ± 0.039 3) 0.006 ± 0.003 4) 0.007 ± 0.007	N/A	N/A
qPCR: No sig difference between 1 and 2, except lower A naeslundii count in 1 Live *P gingivalis* cells sig lower in 1 than 3 Live *A actinomycetemcomitans* cells lower in 1 and 2 than in 3 After regrowth: 1) Sig less than 2 regrowth in biofilm for all species except *A actinomycetemcomitans* and *S oralis* 1) Lowest ratios for most species	SEM 1) Displayed attached particles of ≈ 0.1 µm firmly attached to the implant surface	N/A
SEM and CFU: Longer application time led to higher surface cleaning vs untreated biofilm 3 and 4) Similar CFU counts	N/A	N/A
SEM: Biofilm removal (%): 1) 94.9 2) 52.1 3) 95.3	SEM No post-tx alterations (eg, crater-like defects or scratches); ie, no tx led to surface feature changes	N/A
a and b) surfaces: Decontamination with 1 sig better than 2 Biofilm removal (SEM) 1 (99.9% and 94) and 3 (95.9% and 88.5%) greater decontamination than 2 (81% and 43%)	LCPM and SEM: Surfaces a and b): No tx led to surface changes	N/A
CFU 3) > 90% biofilm removal 3 > 4 > 1 > 2 > 6 > 5	OCP: 3 and 4) Most stable behavior (–0.09 V) after stabilization 2) Most unstable surface with highest corrosive dissolution potential (–0.15 V) and highest Ti dissolution SEM and AFM: surface morphology: 2) Led to surface alterations ("valleys" and pits) linked to generation of Ti wear microparticles 1, 3, 4) Least aggressive intervention; no surface Ti mechanical abrasion	1), 3), 4) highest live cell counts 3 and 4) Proliferation sig higher than controls 2) Sig fewer viable cells proliferating vs 5 6) Lowest live cell counts and sig more dead cells vs controls

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Appendix Table 3 *(cont)* **Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies**

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Leung et al[114] (2021)	Ti discs (N/A) SLA	Discs incubated in medium with subgingival plaque samples from 1 volunteer with healthy periodontium in medium in anaerobic conditions at 37°C (21 d)	1) APA (25% glycine) – 3 mm distance 2) APA (50% glycine) – 3 mm distance 3) APA (50% glycine) – 6 mm distance 4) Air abrasion without any powder – 3 mm distance 5) No tx	SEM
Namour et al[115] (2021)	72 TiZr discs SLActive	Discs incubated in medium with 14-species community in microaerophilic conditions (48 h)	1) Q-Switch Nd:YAG laser (270 mW) (2 s) 2) Contaminated, no tx 3) Sterile, no tx	CFU
Schuldt et al[116] (2021)	56 Ti discs SLA	Discs incubated in medium with subgingival plaque samples from 1 volunteer with healthy periodontium in anaerobic conditions at 37°C (21 d)	1) Discs rinsed and immersed in in medium (48 h) (control) 2) L-PRF applied and immersed in medium (48 h) 3) Undisturbed original biofilm	SEM (bacteria/ unit area)
Alovisi et al[117] (2022)	45 Ti discs 21 machined 24 SLA	Discs incubated in medium with saliva from 10 volunteers and polymicrobial biofilm (6) in anaerobic conditions at 37°C (24 h)	1) Contaminated, nontreated 2) atb gel (ciprofloxacin, metronidazole, clarithromycin) (1 h) 3) APA (glycine) (1 min) 4) atb gel and APA	SEM Cell growth (mesenchymal stem cells) Live/dead stain
Citterio et al[118] (2022)	43 implants Dual acid-etched Crater-like peri-implant defect model	Implants incubated in medium with saliva from 10 volunteers with healthy periodontium and polymicrobial biofilm (7) in anaerobic conditions at 37°C (64 h)	1) Contaminated, nontreated 2) Air abrasion without any powder 3) APA (erythritol) 4) Sulfonic/sulfuric acid gel 5) APA and sulfonic/sulfuric acid gel 6) Noncontaminated, nontreated	CFU Osteoblast-like cell regrowth
Fronchetti Junior et al[119] (2022)	16 Ti implants Immobilized by titanium forceps	Implants incubated in a medium with subgingival biofilm from periodontitis patient (time N/A)	1) Noncontaminated, nontreated Implants were brushed with a toothbrush and saline solution (20 brush strokes), then: 2) Contaminated, nontreated 3) APA (sodium bicarbonate) (30 s) 4) APA (sodium bicarbonate) (60 s)	CFU SEM
Kamionka et al[120] (2022)	140 discs a) Anodized b) SA	Discs incubated in medium with plaque samples from 1 volunteer with periodontitis at 37°C (7 d)	1) APA (glycine) (90 s) 2) APA (erythritol) (90 s) 3) Argon CAP (9 min) 4) APA (glycine) and argon CAP 5) APA (erythritol) and argon CAP 6) Contaminated, untreated 7) Sterile discs	SEM Fluorescence microscopy

Residual bacteria/deposits	Surface alterations	Cell culture
SEM: 2) 7.7 cells/field 4) 169.3 cells/field No sig difference between: 2 and 3 1 and 2	N/A	N/A
Log10 CFU/mL: 1) 0 2) 5×10^3 3) 0	N/A	N/A
SEM: 1) 151 ± 82 bacteria/field 2) Reduced by 92.1%; 40% of the specimens had 0 bacteria/field	N/A	N/A
Dead bacteria (%) in a: 2) ~ 18 3) ~ 24 4) ~ 45 Dead bacteria (%) in b: 2) ~ 76 3) ~ 82 4) ~ 95 In a and b surfaces, % dead bacteria sig higher in 4; decontamination sig better in 4a than 4b	N/A	Cell adhesion and growth (72 h): 4b) Sig better than 3b, 2b, and 4a
Log_{10} CFU/mL: 1) 10^7 2) 10^7 3) 10^7 4) 10^3 5) 10^3	N/A	Osteoblast-like cells coverage (%): 1) 7.4 ± 4.8 2) 12.4 ± 4.4 3) 24.1 ± 6.7 4) 33.5 ± 11.3 5) 51.7 ± 9.5 6) 60.1 ± 9.3
Log10 CFU/mL: 1) 0.7×10^1 2) 5×10^6 3) 4×10^6 4) 3×10^6 3 and 4) Sig less CFU counts than 2 but could not completely eliminate the microbial biofilm 4) Sig better than 3	SEM 3 and 4) No changes on implant surfaces; no presence of fractures and cracks or visible changes compared with 1 and 2	N/A
1 and 2) 2 times more biofilm on a) than b) surfaces Reduction of biofilm (%) after 5 d: surfaces a / b: 1) 35.1 / 55.1 2) 31 / 86 3) 16.1 / 13.9 4) 78.7 / 90.6 5) 77.2 / 89.5 6) N/A 7) 70.5 / 92.2	N/A	N/A

Appendix Table 3 *(cont)* **Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies**

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Matthes et al[121] (2022)	84 Ti discs SA	Discs incubated in medium with plaque from 1 volunteer with periodontitis at 37°C (7 d)	1) Stainless steel CUR and cotton swab 2) Water jet 3) Combination of 1 and argon CAP 4) Combination of 2 and argon CAP 5) Contaminated (negative control) 6) Noncontaminated (positive control)	Biofilm regrowth (discs incubated after tx [96 h)] Turbidity SEM after osteoblast-like cells culture Wettability (water contact angle)
Sousa et al[122] (2022)	36 Ti discs a) SLA b) Machined Placed in disc holder	Discs incubated in medium with pooled saliva (time N/A)	1) Ti brush (60s) 2) Ti brush and PDT 3) Ti brush and 0.2% CHX/1% NaClO 4) Ti brush and ultraviolet-C radiation 5) Ti brush and PDT and ultraviolet-C radiation 6) Ti brush and 0.2% CHX/1% NaClO and ultraviolet-C radiation 7) Contaminated, nontreated 8) Noncontaminated, nontreated	SEM CFU Surface topography Wettability EDX Cell culture (human osteoblast-like osteosarcoma)
Stein et al[123] (2022)	153 Ti discs 153 Zi discs Ti: corundum-blasted and acid-etched Zr: yttria-stabilized Zr	Discs incubated in medium with 6 bacterial species and sterile saliva in anaerobic conditions (7 d)	Mechanical (20 s): 1) Ti CUR 2) Stainless steel US 3) APA (glycine) 4) APA (erythritol) 5) Er:YAG laser Chemical submersion (2 min) in: 6) 1% CHX 7) 10% povidone-iodine 8) 14% doxycycline 9) 0.95% NaOCl 10) Untreated control	SEM Live/dead stain (rRNA counts – bacterial activity) Cell culture (human fibroblasts) XPS
Vaddamanu et al[124] (2022)	Ti discs SA Plastic models	Discs incubated in medium with 9 bacterial species (3.5 d)	1) Er:YAG laser 2) PDT 3) Ti CUR 4) Ti CUR and PDT	CFU Cell culture (osteoblasts)
Zipprich et al[125] (2022)	60 implants SLA	Implants incubated in medium with saliva from 3 volunteers with healthy periodontium at 37°C (14 d)	1) APA (erythritol) 2) Diode laser – PDT 3) Plasma cleaning (argon) 4) Electrolytic cleaning with potassium iodide (KI) 5) Electrolytic cleaning with sodium formate (CHNaO2) 6) Untreated control	Test area on implant surface: a) Favorable access (coronal and parallel) b) Angled surface (apical and tilted to implant axis) Live/dead bacteria
Alonso-Espanol et al[126] (2023)	105 implants SLA	Discs incubated in medium with 6 bacterial species in anaerobic conditions at 37°C (72 h)	Implants immersed (60 s) into: 1) Phosphate-buffered saline 2) CHX 3) Dimethyl sulfide 4) Xanthohumol 5) Curcumin	SEM qPCR

Residual bacteria/deposits	Surface alterations	Cell culture
Biofilm regrowth (96 h): 1) 1.210 2) 1.189 3) 0.252 4) 0 5) 1.242 6) N/A SEM: crossing points with microbes (%): 1) 12.2 ± 27.1 2) 27.7 ± 33.8 3) 0.6 ± 2.8 4) 0 ± 0.1 5) 53.7 ± 31.5 6) 0 ± 0.1	Wettability: water contact angle 2 h after tx (degrees): 1) 50 2) 68 3) 17 4) 22	Crossing points with cells (%) 1) 10 ± 26.9 2) 11.4 ± 29.4 3) 71.9 ± 37.5 4) 82 ± 31 5) 0 ± 0 6) 78.5 ± 31.4
CFU/mL: Sig decrease in viable counts in all tx groups (1, 2, 3, 4, 5, 6) vs 7 Only tx 1 left detectable live bacteria behind	Surface roughness: 4–6) < roughness Wettability: 4–6) < contact angles in a, less in b EDX: 4–6) surfaces > O% < C%	Cell culture (7 d): UV-C radiation > cell proliferation
SEM: Ti discs: All tx did not lead to sig difference to 10 SEM: Zi discs: 2, 3 and 4) Sig higher reductions vs 10 rRNA counts: Ti discs: 2, 3, 4, and 5) Sig reductions in counts 9) Led to sig reductions rRNA counts: Zr discs: 2, 3, 4, and 5) Sig reductions in counts, more pronounced than Ti surfaces	XPS: %Ti on Ti discs: slightly > with 2, 3, and 4 Control and others had 0%, could be insufficient decontamination After 3 and 4: %Si (part of APA powders) found XPS: %Zr on Zr discs: 3, 4, and 9) Led to increased sig; increased biofilm reduction	Cell viability 1–5) Highest viability and low cytotoxicity Cytotoxic effect: 6) 41% on Ti, 27% on Zr discs 7) Low cytotoxicity Alive/dead: 6) Sig < no. of viable cells and > no. of dead cells
CFU: 1) Sig eradication of biofilm > 2, 3, 4	N/A	Cell culture: 1) Osteoblasts adhered in sig advanced quantity
Decontamination was sig better in a than b Alive/dead bacteria (%) in a): 1) 2 / 1 2) 14 / 9 3) 24 / 9 4) 0 / 0 5) 0 / 0 6) 56 / 31 Alive/dead bacteria (%) in b): 1) 30 / 12 2) 24 / 11 3) 28 / 11 4) 0 / 0 5) 0 / 0 6) 57 / 33	N/A	N/A
SEM: 4 and 5) Resulted in a clear < in the microbial density of the biofilms in comparison with 1 or 3. qPCR: The 6 bacterial species reduced sig after 4 or 5; no sig difference to 2	N/A	N/A

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Appendix Table 3 *(cont)* **Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies**

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Ichioka et al[127] (2023)	123 implants Blasted and treated with fluoride ions Placed in crater-like peri-implant defect model	Implants positioned in sterile 24-well cell culture plate and immersed in saliva at 37°C for pellicle development (4 h), then inoculated with bacterial suspension in anaerobic conditions at 37°C (72 h)	60 s: 1) Gauze soaked in 0.9% saline 2) Gauze soaked in alkaline-electrolyzed water 3) Gauze soaked in N-acetyl-L-cysteine 4) APA (erythritol) and gauze soaked in 0.9% saline 5) APA (erythritol) and gauze soaked in alkaline-electrolyzed water 6) APA (erythritol) and gauze soaked in N-acetyl-L-cysteine 7) Rotating NiTi brush and gauze soaked in 0.9% saline 8) Rotating NiTi brush and gauze soaked in alkaline-electrolyzed water 9) Rotating NiTi brush and gauze soaked in N-acetyl-L-cysteine 10) Contaminated, no tx 11) Sterile implant (control)	SEM EDS qPCR
Matthes et al[128] (2023)	Implants (N/A) Grit-blasted and high-temperature-etched Placed in special holder	Discs incubated in medium with plaque samples from 1 volunteer with periodontitis at 37°C (7 d)	1) Cotton gauze 2) Water jet 3) Combination of 1 and argon CAP 4) Combination of 2 and argon CAP 5) Contaminated (negative control) 6) Noncontaminated (positive control)	SEM CFU after rolling the implants on agar plates
Tran et al[129] (2023)	189 pure Ti discs a) SLA b) Abraded c) Polished	Discs incubated in saliva from 1 donor and medium in anaerobic conditions (96 h)	1) APA (glycine) (15 s) 2) APA (sodium bicarbonate) (15 s) 3) APA (calcium carbonate) (15 s) 4) Piezo US with Ti tip (30 s) 5) Carbon CUR (30 s) 6) Ti CUR (30 s) 7) NiTi brush (30 s) 8) 40% citric acid and cotton swab (60 s) 9) Untreated	SEM (crystal violet assay)
Virto et al[130] (2023)	9 Ti-Zr implants SLA	Implants incubated in pooled bacterial culture in anaerobic conditions at 37°C (up to 72 h)	Electrochemical decontamination (VersaSTAT): Anodic polarization: 1) 0.75 V 2) 1.5 V 3) 3 V Cathodic polarization 4) –0.75V 5) –1.5V 6) –3 V 7) Immersed in electrolyte without any potential (control)	SEM Live bacteria Electrolytes

Residual bacteria/deposits	Surface alterations	Cell culture
SEM: Area of residual bacteria 1, 2, and 3) Abundance of residual bacteria was observed, especially in the intrabony zone (2161, 1828, 1996 μm^2) 4, 5, and 6) Sig reduction (524, 266, 425 μm^2) 7, 8, and 9) Sig reduction (535, 805, 962 μm^2) Intrabony zones sig > supracrestal macro- and microthread Top and flank sites sig > valley sites qPCR (CFU/mL): All tx groups: Sig reduction of all 6 species by ≥ 1 order of magnitude No difference among groups	SEM 1, 2, and 3) Remaining gauze fibers occasionally detected 4, 5, and 6) Neither powder-like deposits nor notable surface damage evident 7, 8, and 9) Remarkable alterations in surface morphology: scratch marks at top and flank sites in macro- and microthreaded zones EDS: %C: %C < all tx groups vs 10; 1 sig > than other tx; 4– 9 sig reduction EDS: %O: 4) r4 reached pristine levels ~11) EDS: %Ti: Sig increased after decontamination	N/A
SEM 2 and 4) comparable to 6 CFU 4) Outperformed 1, 2, 3	SEM Scratched surface area visible in all mechanically treated implants (1.9% in 1 to 3.8% in 4)	N/A
SEM: Crystal violet assay: All tx led to > 80% sig biofilm reduction, irrespective of surface type 1) Eliminated the most biofilm (94.8%–96.1%), sig better than all other tx 3) Second most effective tx 5, 6, and 7) Least effective at eliminating biofilm across all surfaces 8) Comparable to mechanical debridement instruments	SEM 1) No discernible surface alterations 2a) Minor surface changes to roughness 2b) No discernible changes 2c) Occasional abrasive particles embedded into surface, no scratches 3) Abrasive particles embedded into a), scratch marks on surface 4) Gross damage across all surfaces; c: grooves; a and b: flattening of projections 5 and 6) considerable changes to surface morphology, flattening of projections in a and b 7) Gross modifications to all surfaces; a: flattening of projections; c: scratching 8) Little to no surface change	N/A
SEM: Live bacteria: Sig reductions at 3 ($1.8 \times 10^5 \pm 1.9 \times 10^5$; 94.1%) and 6 ($2.9 \times 10^4 \pm 2.6 \times 10^4$; 99.1%) vs 7 ($3.1 \times 10^6 \pm 5.7 \times 10^6$) 1–6) *F nucleatum* most affected	Oxidation assays (initial pH = 6.4): 1) 6.9 ± 0.9 2) 6.9 ± 0.5 3) 8.1 ± 0.7 1 and 2) Led to no evident changes in the electrolyte 3) Turned to an orange hue coming from the implant Reduction assays (initial pH = 6.4): 4) 6.5 ± 0.1 5) 6.6 ± 0.2 6) 10.9 ± 0.3 4) No changes in electrolyte, implant surface, or mesh 5) Bubbling phenomenon affecting implant surface 6) Reddish precipitate diffused between electrodes and almost covered the entire recipient after 5 min of tx	N/A

Appendix Table 3 *(cont)* **Biofilm Decontamination of Implant and Disc Surfaces: In Vitro Studies**

Study	No., type, and surface of discs/implants	Biofilm	Treatment (decontamination method)	Evaluation technique
Costa et al[131] (2023)	Ti discs Rough	Implant contamination with multispecies biofilm from saliva from 4 volunteers incubated at 37°C with 10% CO2 (48 h)	Mechanical: 1) Ti CUR 2) Teflon CUR 3) Ti brush 4) Water jet 5) Er:YAG laser Chemical: 6) Iodopovidone 2% 7) Amoxicillin 8) Minocycline 9) Tetracycline 10) H_2O_2 3% 11) CHX 0.2% 12) HCOBc 13) NaOCl 0.95% Control: 14) Contaminated, not treated	SEM CFU Surface roughness Ti particles release Corrosion rate
Zhu et al[132] (2024)	Ti discs Large-grit sandblasted, double acid-etched	Discs incubated in pooled 6-species bacterial culture in anaerobic conditions at 37°C (up to 72 h)	1) Ti brush 2) US stainless steel tip 3) US PEEK tip 4) APA (erythritol) 5) Electrolytic cleaning (0.6A) (5 min) 6) Contaminated (positive control) 7) Sterile (negative control)	SEM CFU LPS residues Cell culture (bone marrow mesenchymal stem cells) Wettability XPS

APA = air powder abrasive; atb = antibiotic; BioCaP = biomimetic calcium phosphate; Ca = calcium; CAP = cold atmospheric plasma; CFU = colony forming units; C% = percentage (proportion) of carbon; CO2 = carbon dioxide (laser); CUR = curette; d = day; EDS = energy dispersive spectroscopy; EDTA = ethylenediaminetetraacetic acid; Er,Cr:YSGG = erbium, chromium: yttrium-scandium-gallium-garnet (laser); Er:YAG = erbium: yttrium-aluminum-garnet (laser); h = hour; HA = hydroxylapatite; HCOBc = hydrocarbon-oxoborate-based antiseptic; H_2O_2 = hydrogen peroxide; hOBs = human osteoblasts; LM = light microscopy; L-PRF = leukocyte- and platelet-rich fibrin; LPS = lipopolysaccharides; min = minute; N/A = not applicable or not available; NaOCl = sodium hypochlorite; Nd:YAG: neodymium-doped yttrium-aluminum-garnet (laser); O% = percentage (proportion) of oxygen; PEEK = polyetheretherketone; s = second; Saos-2 = "sarcoma osteogenic' cell line; SEM = scanning electron microscopy; sig = significant(ly); SA = sandblasted and acid-etched; SLA = sandblasted large-grit acid-etched; SLActive = modified sandblasted large-grit acid-etched; TCP = tricalcium phosphate; Ti = titanium; Ti% = percentage (proportion) of titanium; Ti-Zr = titanium-zirconium; TiB = titanium brush; TiO2 = titanium dioxide; TiUnite = a slightly negatively charged titanium oxide; tx = treatment; US = ultrasonic scaler; VAS = visual analog scale; W = watts; XPS = x-ray photoelectron spectroscopy; Zr = zirconia.

Residual bacteria/deposits	Surface alterations	Cell culture
CFU: Residual biofilm: No tx led to total biofilm eradication Mechanical: 4 and 5) Sig reduced CFU compared to control (10^3 for both vs 10^7) 3, 4, and 5) Dislodged bacteria in valley areas Chemical: 13) Best antimicrobial protocol, followed by 12; 6- and 5- fold decrease in bacteria viability vs control 6) Sig enhanced 13, should be combined	SEM: 1, 2, and 3) Sig surface damage and peak flattening 4) No evident surface alterations 5) Overall polished appearance with reduced sharpness of peaks, valley areas appeared unaffected Surface roughness: No difference between tx groups Corrosion rate: 5) Reduced Ti% > after 3	N/A
SEM: 1, 2, and 3) Certain no. of bacteria 4) Small no. of bacteria "hidden" CFU: 1, 2, 3, and 4) Live bacteria 5) Bacteria with no activity Residual LPS: 5 < 4 < 2 < 3 < 1 Sig difference btw: a) 5 vs other tx b) 4 vs 2 c) 4 vs 3 d) 2 vs 3	SEM: 1 and 2) Damaged surface to varying degrees, leaving strip and chunky scratches, respectively 2) Most serious, revealing color of Ti substrate 3) 20- to 80-µm-sized flakes on surface, PEEK residual foreign bodies 4) Much residual powder 4 and 5): Surface no different than 7 Contact angle (degrees): 1) 13.2 2) 13.5 3) 35.6 4) 9.5 5) 0 (superhydrophilic) 6) 66.9 XPS: C%: 1, 4, and 5 = 7	Cell culture (24h): 2) Cells with polygonal and highly spreading morphology 3 and 5) Cells with narrow arrangement of actin microfilaments and less spread morphology 1 and 4) Cells did not fully spread Cell culture (7 d): 5 > 2, 3, and 4

MORE DETAILED INFORMATION ON MATERIALS AND METHODS

Eligibility criteria

Inclusion criteria

- Publications reporting on surgical decontamination procedures conducted in animal models with induced peri-implantitis, assessing reosseointegration outcomes
- Human studies assessing reosseointegration following the treatment of peri-implantitis by block biopsy
- Publications in which failed implants due to peri-implantitis were decontaminated prior removal or in the laboratory (ex vivo studies)
- Publications in which discs or implants were exposed to the oral cavity with the aid of stents to form robust standardized biofilms and decontaminated in the laboratory (in situ studies)
- In vitro studies including implants or discs contaminated with human saliva or a multispecies biofilm based on human biofilm or saliva samples or ≥ 6 bacterial strains and decontaminated in the laboratory
- Complete description of decontamination method utilized as well as number of implants/discs treated

Exclusion criteria

- Animal studies focusing solely on the induction of peri-implantitis
- Animal studies in which peri-implantitis was surgically induced rather than plaque-induced
- Animal studies that only involve non-surgical decontamination interventions

Relevant journals, reference lists and citations, and previous systematic reviews were manually searched to identify articles. Studies published without restrictions concerning time and language were initially considered.

Selection Process

Titles and abstracts of the identified articles were assessed independently and in duplicate by two calibrated reviewers (AR and MMB) with the aid of an online software (Rayyan app for systematic reviews). The same tool was used to detect and consider duplicate publications. Any disagreements during study selection were solved through open discussion and whenever a consensus could not be reached, the final decision was made by a third author (DRD). Subsequently, two reviewers (AR, MMB) conducted a thorough full-text reading to confirm study eligibility based on the inclusion and exclusion criteria. The inter-reviewer agreement (percentage of agreement and kappa correlation coefficient) for the two stages were calculated. Reasons for exclusion after full text analysis were recorded.

Data Extraction

Using a predetermined data extraction spreadsheet, the following information was extracted from included studies:

- For animal and human block biopsy studies: General information [first author; year of publication; details and n of animals (species and age) or patients; implant characteristics (brand, surface, diameter, length, material); distribution of implants per animal/patients]; Peri-implantitis and interventions [peri-implantitis model (type of ligature, time); decontamination methods; therapy (resective, regenerative approaches including the use of membranes or bone grafts); healing (submerged or non-submerged healing; time)]; Outcomes [reosseointegration (primary outcome; measured as the percentage of bone to implant contact [BIC] on histological slides); vertical bone gain (histological measurements)].
- For the ex vivo/in situ experiments: General information [first author; year of publication; patients and implants/discs (number of discs or implants, number of patients); type of experimental model (where discs/implants were contaminated and assessed)]; Interventions [decontamination methods; evaluation techniques]; Outcomes [residual bacteria (measured by CFU, percentage of residual biofilm, and others); implant surface (topography, wettability, corrosion, and others); cell culture (osteoblasts, fibroblasts)].
- For the in vitro experiments: General information [first author; year of publication; patients and implants/discs (number of discs or implants, number of patients); type of biofilm]; Interventions [decontamination methods; evaluation techniques]; Outcomes [residual bacteria (measured by CFU, percentage of residual biofilm, qPCR, and others); implant surface (topography, wettability, corrosion, and others); cell culture (osteoblasts, fibroblasts)].

Risk of Bias (RoB)

The risk of bias in the included preclinical in vivo experiments was assessed independently and in duplicate by two review authors (AR and DRD) using the SYRCLE's tool.[1]

Data Synthesis

Owing to the considerable heterogeneity observed among the studies in both the search methodology and the collected data, statistical analysis was precluded. The resultant data set was organized employing a descriptive approach to provide a comprehensive account of the findings.

RESULTS

Study Selection for Each PICO Question

For animal and human block biopsy studies, electronic literature search identified a total of 481 articles (PubMed: 239; Embase: 77; Cochrane: 25; Web of Science: 33; Scopus: 107). Following duplicate removal, 423 records were screened for titles and abstracts, and 43 articles were selected for full-text analysis (κ = 0.898 [CI 95%: 0.724–0.976]). Eighteen additional articles were added through manual screening. From these publications, 15 were excluded for various reasons (Appendix Table 4). Therefore, 46 publications reporting on 41 animal experiments and 5 human block biopsy studies were included.[2–49] Two animal cohorts were reported in two different publications.

For ex vivo and in situ studies, initial search led to a total of 270 articles (PubMed: 65; Embase: 32; Cochrane: 9; Web of Science: 21; Scopus: 143). Following duplicate removal, 223 records were screened for titles and abstracts, and 33 articles were selected for full-text analysis (κ = 0.912 [CI 95%: 0.776–0.994]). Six additional articles were added through manual screening. All full-text publications were included, resulting in 17 ex vivo and 22 in situ experiments.[50–88]

For in vitro studies, initial search led to a total of 679 articles (PubMed: 119; Embase: 77; Cochrane: 10; Web of Science: 184; Scopus: 289). Following duplicate removal, 461 records were screened for titles and abstracts, and 46 articles were selected for full-text analysis (κ = 0.895 [CI 95%: 0.711–0.975]). Nineteen additional articles were identified through manual screening. From these publications, 29 were excluded for various reasons (see Appendix Table 4). Therefore, 36 in vitro experiments were included.[89–124]

A total of 121 publications were included in the present review. The electronic search for preclinical, ex vivo/in situ (grouped) and in vitro studies is shown in Appendix Figure 1. The outcomes investigated in the present review according to the type of study is illustrated in Figure 1.

Risk of Bias

In 22 out of 41 animal studies, at least half of the criteria/domains were either not reported (i.e., unclear risk of bias) or not adequately addressed (i.e., high risk of bias) (Appendix Table 5).

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QUESTION 1: Animal and human studies			
Database	**Search**	**Results**	**Date**
PubMed	((((((((Models, Animal) AND (Induced peri-implantitis)) OR (peri-implantitis)) OR (peri implantitis)) OR (periimplantitis)) AND ((((decontamination [MeSHTerms]) OR (decontamination [Title/Abstract])) OR (decontam* [Title/Abstract])) OR (implantoplasty [Title/Abstract])) OR (detoxification [Title/Abstract])) OR (mechanical [Title/Abstract])) OR (chemical [Title/Abstract])) OR (electrolytic [Title/Abstract]))))) AND (((((surgical) OR (open flap debridement)) OR (resective)) OR (regenerative)) OR (reconstructive))) AND (((((bleeding on probing) OR (probing depth)) OR (bone gain)) OR (bone level))))) AND ((((Histomorphometric) OR (Histomorphometry analysis)) OR (bone to implant contact)) OR (Re-osseointegration))	239	09/03/23
Embase	(('animal experiment'/exp OR 'animal experiment' OR 'animal experimentation' OR 'animal physical conditioning' OR 'animal studies' OR 'animal study' OR 'animal trial' OR 'experiment, animal' OR 'physical conditioning, animal') AND 'induced peri-implantitis' OR 'ligature model' OR 'dental implant') AND ('decontamination'/exp OR chemical OR 'detoxification'/exp OR 'open debridement') AND ('osseointegration'/exp OR 'healing'/exp OR 'bone to implant contact'/exp OR 'bacterial load' OR 'implant surface' OR 'oral biofilm'/exp) AND (animal OR 'ex vivo study'/exp)	77	09/03/23
Cochrane	#1: (peri-implantitis):ti,ab,kw OR (implant surface):ti,ab,kw OR (biofilm):ti, ab, kw #2: (decontamination):ti,ab, kw OR (mechanical):ti,ab,kw OR ("detoxification"):ti,ab, kw OR (electrolytic):ti,ab, kw OR (debridement):ti,ab, kw OR (implantoplasty):ti, ab,kw OR (resective) ti,ab,kw OR (regenerative):ti, ab,kw OR (reconstructive):ti,ab,kw #3: (animal):ti, ab, kw OR ("ex vivo"):ti, ab,kw OR (induced peri-implantitis):ti,ab, kw #1 AND #2 AND #3	25	09/03/23
Web of Science	1: (((ALL=(induced peri-implantitis)) OR ALL=(peri-implantitis)) OR ALL=(ligature model)) 2: (((((ALL=(decontamination)) OR ALL=(detoxification)) OR ALL=(mechanical)) OR ALL=(chemical)) OR ALL=(implantoplasty)) OR ALL=(electrolytic) 3: ((((ALL=(surgical)) OR ALL=(open flap debridement)) OR ALL=(resective)) OR ALL=(regenerative)) OR ALL=(reconstructive) 4: ((((ALL=(histomorphometry)) OR ALL=(histomorphometric)) OR ALL=(bone to implant contact)) OR ALL=(re-osseointegration)) OR ALL=(bone gain) 5: ((ALL=(animal)) OR ALL=(experimental)) #1 AND #2 AND #3 AND #4 AND #5	33	04/20/24*
Scopus	ALL (animal) OR ALL (dog) OR ALL ("pre-clinical") AND ALL ("induced peri-implantitis") OR ALL ("ligature model") AND ALL (decontamination) OR ALL (detoxification) OR ALL (mechanical) OR ALL (chemical) OR ALL (implantoplasty) OR ALL (electrolytic) AND ALL (surgical) OR ALL ("open flap debridement") OR ALL (resective) OR ALL (regenerative) OR ALL (reconstructive) AND ALL (histomorphometry) OR ALL (histomorphometric) OR ALL ("bone to implant contact") OR ALL (re-osseointegration) OR ALL ("bone gain") AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (clinical)	107	04/20/24*

*The search on Web of Science and Scopus was performed for papers published up to February 2024.

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QUESTION 2: Ex vivo and in situ studies			
Database	**Search**	**Results**	**Date**
PubMed	("biofilm s"[All Fields] OR "biofilmed"[All Fields] OR "biofilms"[MeSH Terms] OR "biofilms"[All Fields] OR "biofilm"[All Fields]) AND ("removability"[All Fields] OR "removal"[All Fields] OR "removals"[All Fields] OR "remove"[All Fields] OR "removed"[All Fields] OR "removement"[All Fields] OR "remover"[All Fields] OR "removers"[All Fields] OR "removes"[All Fields] OR "removing"[All Fields]) AND (("titanium"[MeSH Terms] OR "titanium"[All Fields] OR "titaniums"[All Fields]) AND ("decontaminant"[All Fields] OR "decontaminants"[All Fields] OR "decontaminated"[All Fields] OR "decontaminates"[All Fields] OR "decontaminating"[All Fields] OR "decontamination"[MeSH Terms] OR "decontamination"[All Fields] OR "decontaminate"[All Fields] OR "decontaminations"[All Fields] OR "decontaminative"[All Fields]))	65	10/07/23
Embase	(('patient'/exp OR 'dental implant' OR 'implant, teeth' OR 'implant, tooth' OR 'implant, teeth') AND 'peri-implantitis' OR 'periimplantitis' OR 'peri implantitis') AND ('decontamination'/exp OR chemical OR 'detoxification'/exp OR 'open debridement') AND ('bacterial load' OR 'bacterial debris' OR 'contamination' OR 'implant surface' OR 'oral biofilm'/exp) AND ('explantation', OR 'implant removal')	32	10/07/23
Cochrane	#1: (peri-implantitis):ti,ab,kw OR (implant surface):ti,ab,kw OR (biofilm):ti, ab, kw #2: (decontamination):ti,ab, kw OR (mechanical):ti,ab,kw OR ("detoxification"):ti,ab, kw OR (electrolytic):ti,ab, kw OR (debridement):ti,ab, kw OR (implantoplasty):ti, ab,kw OR (removal) ti,ab,kw OR (explantation):ti, ab,kw OR (stent):ti,ab,kw #3: (human):ti, ab, kw OR ("ex vivo"):ti, ab,kw OR ("in situ"):ti,ab, kw #1 AND #2 AND #3	9	10/07/23
Web of Science	1: (((ALL=(peri-implantitis)) OR ALL=(implant surface)) OR ALL=(titanium discs)) 2: (((((((((ALL=(decontamination)) OR ALL=(detoxification)) OR ALL=(mechanical)) OR ALL=(chemical)) OR ALL=(implantoplasty)) OR ALL=(electrolytic) OR ALL=(debridement)) OR ALL=(implant removal)) OR ALL=(explantation)) OR ALL=(stent) 3: (((((ALL=(bacterial load)) OR ALL=(bacterial debris)) OR ALL=(contamination)) OR ALL=(damage)) OR ALL=(surface modification)) OR ALL=(surface alteration) 4: (((ALL=(ex vivo)) OR ALL=(in situ)) AND ALL=(biofilm)) #1 AND #2 AND #3 AND #4	21	04/20/24*
Scopus	ALL (peri-implantitis) AND ALL (decontamination) OR ALL (detoxification) OR ALL (electrolytic) OR ALL (debridement) OR ALL ("implant removal") OR ALL (explantation) OR ALL (stent) AND ALL ("bacterial load") OR ALL ("surface modification") OR ALL ("surface alteration") AND ALL ("ex vivo") OR ALL ("in situ") AND ALL (biofilm) AND NOT TITLE-ABS-KEY (review)	143	04/20/24*

*The search on Web of Science and Scopus was performed for papers published up to February 2024.

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QUESTION 3: In vitro studies			
Database	**Search**	**Results**	**Date**
PubMed	((((((((titanium alloy (TiAl6V4)) OR (titanium)) OR (dental implant)) OR (implant surface)) OR (peri-implantitis)) AND (biofilm)) AND (((((((Bacterial load) OR (wettability)) OR (corrosion)) OR (biocompatibility)) OR (titanium particles)) OR (bacterial counts)) OR (biofilm area))) AND (((((decontamination) OR (mechanical)) OR (decontamin*)) OR (electrolytic)) OR (detoxification))) AND (in vitro)) NOT (review)	119	09/03/23
Embase	('titanium'/exp OR 'ti' OR 'titanium' OR 'titanium alloy' OR 'tooth implant'/exp OR 'dental implant' OR 'dental implants' OR 'implant, teeth' OR 'implant, tooth' OR 'implants, teeth' OR 'implants, tooth' OR 'teeth implant' OR 'teeth implants' OR 'tooth implant' OR 'tooth implants' OR 'implant surface' OR 'periimplantitis'/exp OR 'peri-implantitis' OR 'periimplantitis') AND ('biofilm'/exp OR 'bio-film' OR 'bio-films' OR 'biofilm' OR 'biofilm growth' OR 'biofilm prevention' OR 'biofilms') AND (decontamination OR mechanical OR decontamin* OR electrolytic OR detoxification) AND ('bacterial load'/exp OR 'bacterial burden' OR 'bacterial load' OR 'wettability'/exp OR 'hygroscopicity' OR 'wettability' OR 'corrosion'/exp OR 'corrosion' OR 'corrosion, steel' OR 'biocompatibility'/exp OR 'biocompatibility' OR 'titanium particles' OR 'bacterial counts' OR 'biofilm area') AND ('in vitro study'/exp OR 'in vitro' OR 'in vitro studies' OR 'in vitro study' OR 'in vitro technique' OR 'in vitro techniques')	77	09/03/23
Cochrane	#1: ("titanium"):ti,ab,kw OR (dental implants):ti,ab,kw OR (implant surface):ti, ab, kw OR ("peri-implantitis"):ti, ab, kw AND ("biofilm"):ti, ab, kw #2: (decontamination):ti,ab, kw OR (mechanical):ti,ab,kw OR ("detoxification"):ti,ab, kw OR ("electrolytical"):ti,ab, kw OR (electrolytic):ti,ab, kw #3: (bacterial load):ti, ab, kw OR (wettabillity):ti, ab,kw OR (corrosion):ti,ab, kw OR (biocompatibility):ti,ab, kw OR (titanium particles):ti,ab, kw #4: (bacterial count):ti,ab, kw OR (biofilm area):ti,ab, kw #5: #3 OR #4 #6: ("in vitro assay"):ti,ab, kw OR ("in vitro"):ti,ab, kw OR ("in vitro study"):ti,ab, kw #1 AND #2 AND #5 AND #6	10	09/03/23
Web of Science	1: (((ALL=(titanium)) OR ALL=(titanium alloy)) OR ALL=(dental implant)) OR ALL=(implant surface)) OR ALL=(peri-implantitis)) 2: ALL=(biofilm) 3: (((((((ALL=(decontamination)) OR ALL=(mechanical)) OR ALL=(detoxification)) OR ALL=(chemical)) OR ALL=(electrolytic) 4: (((((ALL=(bacterial load)) OR ALL=(wettability)) OR ALL=(corrosion)) OR ALL=(biocompatibility)) OR ALL=(titanium particles)) OR ALL=(bacterial count)) OR ALL=(biofilm area) 5: ALL=(in vitro) NOT ALL=(review)) OR ALL=(randomized clinical trial) #1 AND #2 AND #3 AND #4 AND #5	184	04/20/24*
Scopus	ALL ("dental implants") OR ALL ("implant surface") OR ALL ("peri-implantitis") AND ALL (biofilm) AND ALL (decontamination) OR ALL (mechanical) OR ALL (detoxification) OR ALL (electrolytic) AND ALL ("bacterial load") OR ALL ("bacterial count") OR ALL ("biofilm area") AND ALL ("in vitro") AND (LIMIT-TO (DOCTYPE, "ar"))	289	04/20/24*

*The search on Web of Science and Scopus was performed for papers published up to February 2024.

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Appendix Table 4 Articles Excluded After Full-Text Analysis and Reasons for Exclusion

Reason for exclusion	Type of study	Studies identified via databases and registers	Studies identified via other methods
No reosseointegration outcomes	Animal/human	Schüpbach et al[1] (1994); Persson et al[2] (1996); Stübinger et al[3] (2005)	Hürzeler et al[4] (1995); Schwarz et al[5] (2014); Ramanauskaite et al[6] (2021); Ramanauskaite et al[7] (2021)
Peri-implant bone defects created with a bur	Animal/human	Nevins et al[8] (2014)	None
No treatment, only biofilm formation	Animal/human	Marinello et al[9] (1995); Zitzmann et al[10] (2004); Carcuac et al[11] (2020); Monje et al[12] (2021); Raimondo et al[13] (2021); Sanz-Esporrin et al[14] (2021); Ko et al[15] (2023)	None
No biofilm but ink to simulate debris on implant surface	In vitro	Wei et al[16] (2017); Keim et al[17] (2019); Tuchscheerer et al[18] (2021); Luengo et al[19] (2022); Giffi et al[20] (2023)	Matsubara et al[21] (2019); Sanz-Martín et al[22] (2021); Korello et al[23] (2023)
Antibacterial and bioactive coatings, not implant decontamination	In vitro	Cochis et al[24] (2015); Ma et al[25] (2017); Aranya et al[26] (2017)	–
< 6 bacterial strains	In vitro	Dennison et al[27] (1994); Kreisler et al[28] (2005); Gonçalves et al[29] (2010); Park et al[30] (2013); Drago et al[31] (2014); Strever et al[32] (2017); Mensi et al[33] (2018); Lee et al[34] (2018); Patianna et al[35] (2018); Toma et al[36] (2018)	Azizi et al[37] (2018); Qin et al[38] (2020); Tonon et al[39] (2020); Balderrama et al[40] (2021); Ichioka et al[41] (2021); Misischia et al[42] (2021); Chackartchi et al[43] (2022); Assuncao et al[44] (2023)

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Appendix Table 5 RoB of the 41 Animal Studies Included and Assessed Using the SYRCLE's Tool

Studies	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
	Sequence generation: *Was the allocation sequence adequately generated and applied?*	**Baseline characteristics:** *Were the groups similar at baseline or were they adjusted for confounders in the analysis?*	**Allocation concealment:** *Was the allocation to the different groups adequately concealed?*	**Random housing:** *Were the animals randomly housed during the experiment?*	**Blinding (investigators and caregivers):** *Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?*	**Random outcome assessment:** *Were animals selected at random for outcome assessment?*	**Blinding (outcome assessor):** *Was the outcome assessor blinded?*	**Incomplete outcome data:** *Were incomplete outcome data adequately addressed?*	**Selective outcome reporting:** *Are reports of the study free of selective outcome reporting?*	**Other sources of bias:** *Was the study apparently free of other problems that could result in high risk of bias?*
Grunder et al[11] (1993)	+	+	+	?	?	?	?	+	+	+
Jovanovic et al[12] (1993)	?	?	?	?	?	?	?	+	+	+
Singh et al[13] (1993)	–	+	–	?	–	?	–	+	+	+
Ericsson et al[14] (1996)	–	+	–	?	–	?	?	+	+	+
Hanisch et al[15] (1997)	+	+	+	+	?	?	?	+	+	?
Hurzeler et al[16] (1997)	+	+	+	?	?	?	+	+	+	–
Persson et al[19] (1999)	–	+	–	?	?	?	?	+	+	+
Wetzel et al[20] (1999)	+	+	?	?	?	?	?	+	+	+
Machado et al[17] (1999)	+	+	+	?	+	?	+	–	+	+
Machado et al[18] (2000)	?	+	+	?	–	+	?	+	+	+
Nociti et al[21] (2000)	+	+	+	?	?	?	?	–	+	+
Deppe et al[22] (2001)	+	+	+	?	?	?	?	?	+	+
Persson et al[23] (2001)	?	+	–	?	–	?	?	+	+	+
Shibli et al[28] (2003)	+	+	+	?	?	?	?	?	+	+
Schou et al[25–27] (2003)	+	+	+	?	?	+	?	+	+	+
Persson et al[29] (2004)	–	+	?	?	–	?	?	+	+	+
Shibli et al[31] (2006)	+	+	+	?	?	?	?	+	+	+
You et al[32] (2007)	+	+	+	?	?	?	?	+	?	?
Parlar et al[33] (2009)	?	+	?	?	?	?	?	+	+	+
Schwarz et al[35] (2011)	+	+	+	?	?	?	+	+	+	+
Albouy et al[34] (2011)	+	+	+	?	?	?	?	+	–	+
Park et al[38] (2015)	–	+	?	?	?	?	?	?	+	+
Shi et al[40] (2015)	+	+	+	?	+	?	+	+	+	+
Namgoong et al[37] (2015)	+	+	+	+	?	?	+	+	+	+
Carcuac et al[36] (2015)	+	+	+	?	–	?	?	+	+	+

Appendix Table 5 *(cont)* **RoB of the 41 Animal Studies Included and Assessed Using the SYRCLE's Tool**

Studies	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
	Sequence generation: *Was the allocation sequence adequately generated and applied?*	**Baseline characteristics:** *Were the groups similar at baseline or were they adjusted for confounders in the analysis?*	**Allocation concealment:** *Was the allocation to the different groups adequately concealed?*	**Random housing:** *Were the animals randomly housed during the experiment?*	**Blinding (investigators and caregivers):** *Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?*	**Random outcome assessment:** *Were animals selected at random for outcome assessment?*	**Blinding (outcome assessor):** *Was the outcome assessor blinded?*	**Incomplete outcome data:** *Were incomplete outcome data adequately addressed?*	**Selective outcome reporting:** *Are reports of the study free of selective outcome reporting?*	**Other sources of bias:** *Was the study apparently free of other problems that could result in high risk of bias?*
Park et al[39] (2015)	?	+	–	?	–	?	+	+	+	+
Htet et al[42] (2016)	+	+	+	?	?	?	+	+	+	+
Carral et al[41] (2016)	+	+	+	+	?	?	+	+	+	?
Machtei et al[43] (2016)	–	+	–	?	–	?	?	+	+	+
Xu et al[44] (2016)	–	+	–	?	–	?	?	+	+	+
Park et al[45] (2017)	–	+	–	?	–	?	+	+	+	+
Ramos et al[46] (2017)	+	+	+	?	+	?	+	+	+	+
Vigano et al[50] (2019)	+	+	+	+	+	?	?	?	+	+
Sanz-Esporrin et al[49] (2019)	+	+	+	?	?	?	?	+	+	+
Morelli et al[48] (2019)	+	+	?	?	–	?	+	+	+	?
Almohandes et al[47] (2019)	+	+	+	?	?	?	+	+	+	+
Yoon et al[51] (2020)	+	+	+	?	?	?	?	+	+	+
Solderer et al[52] (2021)	+	+	–	+	?	?	?	+	+	+
Almohandes et al[53] (2022)	+	+	+	?	?	?	?	+	+	?

The SYCLE tool scores the various domains with a low risk of bias (+), a high risk of bias (–), or an unclear risk of bias (?).

In 22 out of 41 experiments, at least half of the criteria/domains (which are considered as relevant for the reporting of preclinical trials) were either not reported (ie, unclear risk of bias) or not adequately addressed (ie, high risk of bias). Specifically, the domains random housing, blinding (investigator and caregivers), and random outcome assessment were in > 85% of the experiments insufficiently reported or with a high risk of bias.

All references refer to main article reference list.