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REVIEW ARTICLE

Emerging locally delivered antimicrobial and immunomodulatory approaches for the prevention/treatment of peri-implant diseases

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Abstract

Peri-implant diseases are dysbiosis-mediated inflammatory disorders that occur in susceptible hosts. Antimicrobials and immunomodulatory agents therefore might be pertinent as adjunctive measures in the treatment of such disorders. The aim of this narrative review was to examine the existing evidence and assess the effectiveness of emerging locally delivered antimicrobial and immunomodulatory approaches for the prevention/treatment of peri-implant diseases. An electronic search in the PubMed library was carried out to identify traditional and emerging locally delivered antimicrobial and immunomodulatory approaches for the prevention/treatment of peri-implant diseases. A narrative review was conducted to shed light on the role of these approaches to prevent and treat peri-implant diseases. The use of traditional locally delivered antimicrobials as an adjunct to the nonsurgical or surgical treatment of peri-implant diseases has been shown to be safe and effective to a certain extent. Nevertheless, the body of evidence is limited, which precludes the drawing of firm conclusions/recommendations on their daily use for the treatment of these disorders. Likewise, the existing evidence on traditional immunomodulatory approaches is scarce, and so firm conclusions/recommendations on their daily use for the treatment of these disorders cannot be made. Among the emerging antimicrobials and immunomodulatory strategies, argon plasma and lasers seem to offer benefits for the prevention and treatment of peri-implant diseases, respectively. Significant advances have been made in the understanding and potential of novel locally delivered and immunomodulatory approaches for the prevention/treatment of peri-implant diseases. Nevertheless, their clinical application is still limited by a lack of control over the bioactivity afforded by the known delivery systems and the scarcity of consistent nonclinical and clinical data. Awareness must be raised on the part of the industry to develop feasible agents/tools to enhance the efficacy of preventive and therapeutic strategies.

KEYWORDS
dental implant, endosseous implant complication, mucositis, peri-implant disease, peri-implantitis

1 | INTRODUCTION

The understanding of the etiopathogenesis of periodontal and peri-implant diseases has improved considerably thanks to technological breakthroughs in periodontal microbiology and oral immunology. The abundance and function of specific microorganisms are controlled by dynamic changes in the biofilm and its interaction with the host response and microenvironment.[1] These interactions between bacteria and the host influence disease patterns, severity, dissemination, and progression. Plaque accumulation and indices of inflammation on dental implants exhibit a pattern similar to that seen in natural teeth. It is interesting to note that 30 min after implant placement, bacterial colonization takes place.[2] The load of pathogenic bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* increases up to 12 weeks.[2] Between 12 weeks and 12 months, the prevalence of *T. forsythia* tends to increase.[3] Thus, implant sites show a strong susceptibility to exhibit inflammation as a response to the bacterial challenge.

Peri-implant diseases are biofilm-derived inflammatory conditions. It is understood that inflammation is the response to an injurious stimulus and is activated in order to restore homeostasis. Peri-implant mucositis is characterized by the presence of mucosal inflammation, profuse bleeding and/or suppuration on gentle probing (0.15 Ncm), and the absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling.[4] In addition to the presence of bleeding and/or suppuration on gentle probing (0.15 Ncm), peri-implant mucositis is defined by probing depths of ≥6 mm, progressive bone loss, or bone levels ≥3 mm apical to the most coronal portion of the intrabony compartment of the implant (Figure 1).[5] In order to restore peri-implant health, the primary aim is to reduce the pocket depth to levels compatible with maintenance (≤5 mm); otherwise, the likelihood of disease recurrence increases 10-fold.[6] Furthermore, implant surface decontamination and the elimination of pathogens that invade the host tissues are crucial to success in the treatment of peri-implantitis.

It must be taken into account that the microscopic and macroscopic features of contemporary dental implants include grooves, porosities, and undercuts that preclude efficient surface decontamination.[7] It also should be noted that peri-implantitis-related bone lesions are larger compared to periodontitis lesions and extend into the bone marrow.[8] Therefore, the use of antimicrobials might be of interest as an adjunctive measure in the nonsurgical and/or surgical treatment of peri-implantitis. Notably, a randomized clinical trial showed greater pocket depth reduction and substantial marginal bone level gains at 6 months of follow-up using local minocycline in the surgical management of peri-implantitis,[9] while another study demonstrated a significant decrease in pocket depth and an increase in marginal bone level compared to the control group when using local biodegradable, prolonged-release doxycycline in surgical reconstructive treatment after 12 months of follow-up.[10] Likewise,

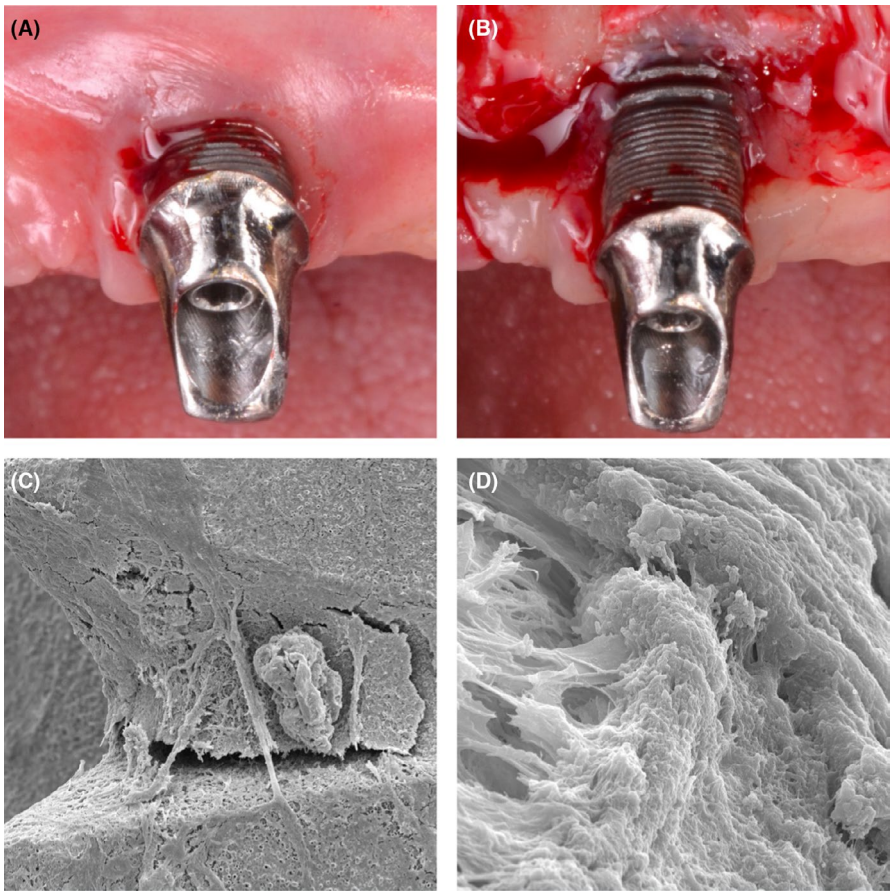

FIGURE 1 Peri-implant diseases are dysbiosis-mediated inflammatory disorders. They commonly (A) manifest with inflammation within the soft tissues, (B) progressive bone loss in the case of peri-implantitis, and (C, D) inflammation is attributed to bacterial contamination of the implant surface.

multiple applications of chlorhexidine chips have been associated with significant improvement of clinical parameters when used as an adjunct to nonsurgical debridement.[11] However, other comparative trials have failed to show the superiority of local antimicrobials when compared to therapeutic strategies that do not involve the use of these agents.[12,13] In fact, when the data were pooled and qualitatively analyzed, the outcomes did not seem to be consistent enough to drive the clinical decision-making process in the treatment of peri-implant disieases.[14,15]

On the other hand, it seems reasonable to propose the use of immunomodulatory agents, given the inflammatory nature of peri-implant diseases, where the ideal outcome of treatment is the restoration of tissue homeostasis, achieved by complete healing through repair of the damaged tissue.[16] The initial acute inflammatory phase transitions into a prolonged unresolved chronic stage with intermittent periods of repair and scarring.[17] The complete clearance of leukocytes from the inflamed tissues is consequently the ideal outcome and requires endogenous activators.[18] While the treatment of chronic inflammation in the case of peri-implant diseases has mostly focused on the removal of bacterial plaque, failure to achieve homeostasis can be attributed to a failure of the immunological response seeking to resolve the inflammation.[19] Accordingly, immunomodulatory strategies are speculated to contribute to disease resolution in a more predictable and effective manner.

2 | TRADITIONAL LOCALLY DELIVERED ANTIMICROBIALS FOR THE PREVENTION/TREATMENT OF PERI-IMPLANT DISEASES

Peri-implant diseases are caused by an inflammatory response to the pathogenic bacterial biofilm. The clinical efficacy of locally delivered antimicrobials (LDAs) in the treatment of peri-implant diseases is emerging.[20–22] LDAs are used as an adjunctive treatment to enhance the effect of mechanical debridement of the implant surfaces that are contaminated by bacteria.[14,15] The most common traditional LDAs are listed in Table 1, and the clinical evidence is displayed in Table 2. Studies treating peri-implant diseases with the aforementioned agents are scarce, but there is evidence from studies treating periodontal diseases. The LDAs most commonly described in the literature are minocycline and doxycycline. They are considered by the United States Food and Drug Administration (FDA) as *"off-label"* drugs for the treatment of peri-implant diseases. However, they can be safely used for implants, considering their microbial and immune contents. Both minocycline and doxycycline are tetracycline derivatives (protein synthesis inhibitor antibiotics) with broad-spectrum action targeting gram-positive and gram-negative microbes, and are also indicated for the treatment of peri-implant mucositis and peri-implantitis. Chlorhexidine, in turn, is a bisbiguanide antiseptic, and is available in Europe as a 0.12% or 0.2% solution, while in the United States it is available as a 0.12% solution or in the form of biodegradable chips. The solution can be irrigated in the peri-implant sulcus, facilitating penetration of the local agent.

TABLE 1 Traditional locally delivery antimicrobial agents (LDAs).

Product	Antimicrobial	Dosage	Delivery system
Arestin	Minocycline HCl	1 mg	Microspheres
Atridox	Doxycycline hyclate	42.5 mg	Polymer
Actisite	Tetracycline HCl	12.7 mg	Fiber
PerioChip	Chlorhexidine gluconate	2.5 mg	Matrix
Elyzol	Metronidazole benzoate	250 mg	Gel
Dentomycin	Minocycline HCl	1 mg	Gel

2.1 | Tetracyclines

In the treatment of peri-implant diseases, the use of LDAs is mainly limited to tetracyclines, including doxycycline or minocycline, as an adjunct to nonsurgical therapy. Mombelli et al, a 12-month case series study, demonstrated that the local treatment of peri-implantitis with tetracycline HCl-containing fibers resulted in a reduction of pocket depth and bleeding on probing.[23] Renvert et al, a randomized controlled trial, showed that treatment in the form of nonsurgical debridement and doxycycline resulted in significantly higher gains in clinical attachment level when compared to mechanical therapy alone.[24] Salvi et al. turn found that the mechanical treatment of peri-implantitis with minocycline hydrochloride as an adjunct resulted in a significant reduction in pocket depth.[26] Emanuel et al. using sustained-release local antibiotic formulated with bone filler in the reconstructive therapy of peri-implantitis, reported promising results in terms of the healing of peri-implantitis lesions.[10]

2.2 | Chlorhexidine

There has been little research on the application of chlorhexidine chips. Sahrmann et al.[27] explored the effectiveness of chlorhexidine chips and gel during supportive peri-implant therapy for the management of mucositis in a randomized controlled trial. Interestingly, chlorhexidine chips were seen to outperform chlorhexidine gel in terms of the reduction of pocket depth and bleeding on probing.[18] For the treatment of peri-implantitis, Machtei et al. found bi-weekly supragingival plaque removal and the local application of chlorhexidine chips for 12 weeks to result in greater mean pocket depth reductions and a greater percentile of sites with pocket depth reductions of ≥2 mm versus bi-weekly supragingival plaque removal alone.[11]

The use of traditional LDAs as an adjunct to the nonsurgical or surgical treatment of peri-implant diseases is safe and effective to a certain extent. Nevertheless, the body of evidence is limited, which precludes the drawing of firm conclusions/recommendations on their daily use for the treatment of such disorders.

TABLE 2 Clinical evidence on the effect of locally delivered antimicrobial agents (LDAs).

	Clinical studies							
Adjunctive therapy	Author	Study type	Follow-up period	Number of patients/ implants	Entity	LDA	Treatment	Treatment outcome
LDDA	Mombelli et al.[23]	Case Series	12 months	25/30	Peri-implantitis	Tetracycline HCl-containing fibers	Nonsurgical mechanical debridement and irrigation with chlorhexidine	Local treatment of peri-implantitis with tetracycline HCl-containing fibers demonstrated reduction in pocket depth and bleeding on probing
	Büchter et al.[24]	Randomized controlled trial	4.5 months	28/48	Peri-implantitis	Doxycycline	Nonsurgical mechanical debridement with curettes	Treatment with nonsurgical debridement + doxycycline resulted in significantly higher gains in clinical attachment level
	Renvert et al.[25]	Randomized controlled trial	12 months	32/NA	Incipient peri-implant infections	Minocycline hydrochloride	Nonsurgical mechanical debridement with curettes and chlorhexidine	Mechanical treatment of peri-implantitis with minocycline hydrochloride as an adjunct demonstrated reduction in pocket depth
	Salvi et al.[26]	Case cohort	12 months	25/31	Peri-implantitis	Minocycline hydrochloride	Nonsurgical mechanical debridement and chlorhexidine	Mechanical treatment of peri-implantitis with minocycline hydrochloride as an adjunct resulted in significant reduction in pocket depth
	Renvert et al.[25]	Randomized controlled trial	12 months	25/31	Incipient peri-implant infections	Minocycline hydrochloride	Nonsurgical mechanical debridement	Mechanical treatment of peri-implantitis with minocycline hydrochloride as an adjunct demonstrated reduction in pocket depth
	Emanuel et al.[10]	Randomized controlled trial	12 months	14/18	Peri-implantitis	Prolonged-release doxycycline	Surgical mechanical debridement and reconstructive therapy with beta-tricalcium phosphate	Sustained-release local antibiotic formulated with bone filler showed promising results in enabling healing of peri-implantitis lesions.

3 | TRADITIONAL IMMUNOMODULATORY APPROACHES FOR THE PREVENTION/ TREATMENT OF PERI-IMPLANT DISEASES

Traditionally, the treatment of peri-implantitis has focused on mechanical debridement to remove plaque and promote healing. However, these methods may not always be sufficient, particularly in advanced cases. This has led researchers and clinicians to explore novel therapeutic approaches, including the use of immunomodulating agents. These are a class of drugs that can modulate the immune response. In the context of peri-implantitis, they could potentially offer a more targeted approach by regulating the inflammatory response. By modulating the immune system, these drugs could help to reduce the excessive inflammation that damages bone tissue, promote healing and tissue regeneration around the implant, as well as enhance the host's ability to fight bacterial infection. Research on the use of locally delivered immunomodulating agents for peri-implantitis is ongoing, with several promising candidates being explored. While further studies are needed to fully establish their efficacy and safety, this emerging field holds great promise for improving the management of peri-implantitis and ensuring the long-term success of dental implants.

3.1 | Tetracycline, synthetic tetracyclines, and chemically modified tetracyclines

Tetracycline is an antibiotic used to treat a wide range of infections due to its broad spectrum of activity. This drug is widely used in periodontology because of the high concentrations it can reach in gingival crevicular fluid. In addition to its antibacterial effect, tetracycline can act as a host-modulating agent by inhibiting matrix metalloproteinase directly, thereby exhibiting an anti-collagenase effect.[28] Moreover, tetracycline can limit the synthesis of certain oxygen metabolites, such as hypochlorous acid, which prevents the breakdown of matrix metalloproteinase inhibitors.[28,29] Other antibiotics in the same class include doxycycline and minocycline.[9,30,31] Doxycycline has drawn particular attention because its anti-collagenase effect is achieved at a lower concentration compared to minocycline and tetracycline. As a result, sub-antimicrobial dose doxycycline (SSD) has been developed to minimize the systemic side effects associated with long-term antibiotic administration. Additionally, doxycycline appears to be more specific, as it blocks matrix metalloproteinase-8 (the collagenase released by polymorphonuclear neutrophils [PMNs]), while having less impact on fibroblast collagenase matrix metalloproteinase-1, which is involved in regular collagen turnover. Systemic sub-antimicrobial doxycycline following the nonsurgical treatment of periodontitis has been tested in different clinical trials, yielding a modest but significant additional pocket depth reduction at 6–9 months after treatment.[30–32] Notably, the adjunctive usage of minocycline to the surgical treatment of peri-implantitis yielded more positive pocket depth reduction and a higher success rate in a 6-month randomized clinical trial.[9] Recently, some chemically modified tetracyclines have been tested, potentially inhibiting matrix metalloproteinases, inducible nitric oxide synthase (iNOS), proinflammatory cytokines, and bone resorption. One major advantage of these modified molecules is that they do not induce gastrointestinal side effects and are effective at lower dosages.

3.2 | Nonsteroidal antiinflammatory drugs

The principal mechanism of action of nonsteroidal antiinflammatory drugs (NSAIDs) is the inhibition of proinflammatory mediators derived from arachidonic acid, notably prostaglandin E2. Prostaglandin E2 is critically involved in periodontal disease, as it significantly enhances osteoclastic activity, thereby contributing to bone resorption and the progression of periodontal tissue destruction.[33,34] By curtailing the production of these mediators, NSAIDs have the potential to modulate the host response. This modulation can lead to a reduction in inflammation and a subsequent decrease in the destructive processes associated with chronic diseases, thereby preserving peri-implant structures.[35] The limited evidence available in the treatment of periodontitis suggests that local and systemic NSAIDs afforded no or very limited clinical benefits.[32] In an early animal study, Weber et al. demonstrated a significant decrease in peri-implant bone loss in comparison to controls following the systemic administration of flurbiprofen.[36] To date, no conclusions can be drawn regarding the efficacy of local NSAIDs in the treatment of peri-implantitis.

3.3 | Bisphosphonates

Bisphosphonates are a class of drugs that have revolutionized the treatment of osteoporosis and bone tumors. Their effectiveness stems from their ability to directly target and inhibit the activity of osteoclasts—the cells responsible for breaking down bone tissue. Bisphosphonates operate through a dual mechanism. Firstly, they induce apoptosis in mature osteoclasts, effectively eliminating these bone-resorbing cells. Secondly, they suppress the differentiation of osteoclast precursors, preventing the transformation of immature precursor cells in the bone marrow into mature osteoclasts, thereby hindering the formation of new bone-degrading cells. This dual action significantly reduces bone resorption, promoting bone density and strength. Additionally, bisphosphonates can indirectly inhibit the activity of matrix metalloproteinases, enzymes that break down the collagen matrix within bones. By chelating essential cations (positively charged ions) like calcium and magnesium, bisphosphonates deprive matrix metalloproteinases of the minerals they need to function effectively.[37]

An early animal study showed systemically administered pamidronate to be effective in inhibiting peri-implant bone loss when peri-implantitis was experimentally induced in beagle dogs.[38] Unfortunately, these drugs have been associated with a potential risk of osteonecrosis of the jaws, and their usage should be carefully

evaluated. Local bisphosphonate gels have also been employed through injection at the base of the periodontal pockets, showing significant pocket depth reductions in comparison to controls.[32] Nevertheless, the current lack of evidence and the potential adverse effects warn against the use of these substances in the routine treatment of peri-implantitis.[39]

3.4 | Statins

Statins, initially developed as a cornerstone therapy for lowering blood cholesterol levels, have emerged as a class of drugs with a surprisingly broad spectrum of effects. Their primary mechanism of action involves inhibition of the enzyme HMG-CoA reductase in the liver, which subsequently reduces the production of cholesterol.[40] However, research has revealed a multitude of additional benefits associated with statin therapy. Beyond cholesterol reduction, statins exhibit potent anti-inflammatory properties by modulating various cellular pathways. They protect the inner lining of blood vessels from damage and dysfunction, demonstrate antioxidant activity by scavenging free radicals, and possess anti-thrombotic effects by modulating blood clotting factors, thereby potentially reducing the risk of blood clot formation. Additionally, statins have immunomodulatory capabilities, interacting with the immune system to influence inflammatory responses, and they may affect bone metabolism, though the exact underlying mechanism is still under investigation.[41–43] Supporting these diverse effects, studies have demonstrated that statins can promote the synthesis of bone morphogenetic protein-2 (BMP-2), which plays a crucial role in bone formation and repair; inhibit the production of interleukin-6 (IL-6) (a key inflammatory cytokine) by macrophages; and reduce the levels of C-reactive protein (CRP), a marker of systemic inflammation[44,45] These findings highlight the multifaceted nature of statins, extending far beyond their cholesterol-lowering properties.

The efficacy of locally delivered statins combined with non-surgical treatment of periodontitis has been assessed in different randomized clinical trials, with promising results.[32] Nevertheless, the use of these drugs in the standard treatment of periodontitis is not recommended, considering the heterogeneity of the results and the high risk of bias of the supporting studies.[39,46] Unfortunately, no clinical trial is available to demonstrate the validity of this approach in the treatment of peri-implant diseases.[46,47] Interestingly, a retrospective study found a negative correlation between the use of systemic statins and bone remodeling.[48]

3.5 | Specialized pro-resolving mediators

Acute inflammation, a critical defense mechanism against infection and tissue injury, is a self-limited process whose timely resolution is essential to prevent tissue damage and promote healing. A specialized family of lipid mediators, collectively termed specialized pro-resolving mediators (SPMs), plays a pivotal role in orchestrating this resolution phase.[18,49,50] SPMs include three main classes: lipoxins, resolvins, and protectins. Lipoxins are derived from arachidonic acid, a fatty acid found in cell membranes. Resolvins and protectins, in turn, are synthesized from omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are abundant in fish oil and share some structural similarities. These SPMs exert potent antiinflammatory and pro-resolution actions through various mechanisms. They promote neutrophil apoptosis, triggering programmed cell death in these white blood cells, which are dominant during the acute phase of inflammation. This prevents neutrophils from causing further tissue damage. SPMs also attract resolution-promoting monocytes by acting as chemoattractants, drawing in specific monocytes that differentiate into specialized resolution macrophages upon reaching the inflamed site. These resolution macrophages play a critical role in clearing debris and promoting tissue repair by actively phagocytosing apoptotic neutrophils, thereby preventing the release of harmful cellular contents. Additionally, SPMs enhance bacterial clearance by directly improving the ability of phagocytes, including macrophages, to engulf and eliminate bacteria at mucosal surfaces, promoting a return to homeostasis.[51–53] By orchestrating these processes, SPMs ensure the timely resolution of inflammation, minimizing tissue damage and facilitating healing. Their therapeutic potential in various inflammatory diseases is currently the subject of intense research.[53]

It seems reasonable that local immunomodulatory drugs may impact positively on the resolution of peri-implant diseases as an adjunct to the mechanical treatment of peri-implantitis. Nonetheless, the existing body of evidence is limited and, therefore, firm conclusions/recommendations on their daily use for the treatment of these disorders cannot be made. Despite their limited clinical application to date, exploration of the use of immunomodulatory strategies is encouraged as an alternative or adjunct to mechanical measures.

4 | EMERGING LOCALLY DELIVERED ANTIMICROBIAL APPROACHES FOR THE PREVENTION/TREATMENT OF PERI-IMPLANT DISEASES

Even though peri-implant diseases are caused by pathogenic bacterial plaque, traditional locally delivered antimicrobial approaches have not demonstrated consistent outcomes in terms of prevention. Some of the main shortcomings of these strategies are their limited sensitivity, ineffectiveness, and brief effect of delivery. For these reasons, exploring emerging approaches using new technologies is important to prevent peri-implant diseases.

4.1 | Implant surface coating/topography

Titanium alloys are widely used as implant materials due to their superior biocompatibility, corrosion resistance, and mechanical properties.[54,55] Various implant surface modifications have been

developed over the years to reduce healing time, increase bone–implant contact, and promote osseointegration.[56,57] However, these modified surfaces have demonstrated a greater susceptibility to bacterial adhesion and the progression of peri-implantitis compared to machined surfaces.[58–62] The interaction between implant surface and bacteria is complex, and several factors are involved, including surface roughness, topography, hydrophilicity, charge, and surface free energy.[63]

Anti-adhesion strategies can be categorized into anti-adhesion coatings and anti-adhesion nano-topographies. The former strategy primarily focuses on minimizing bacterial interaction through the properties of the coating material, while the latter involves artificially imparting anti-adhesive qualities to the implant surface.[63] One common approach involves modifying the hydrophilicity of the materials, as the hydration layer serves as a physical barrier, preventing bacterial attachment by hindering hydrogen bonds and electrostatic interactions with the material surfaces.[64–66] Materials such as polyethylene glycol,[67] zwitterionic polymers,[68] chitosan,[69] hyaluronic acid,[70] and UV-irradiated titanium dioxide coatings can inhibit bacterial adhesion through their hydration layers.[71] Titanium nitride has also been shown to inhibit bacterial interaction due to its chemical and physical properties.[67,72] Additionally, certain substances, such as cinnamaldehyde, can disrupt quorum sensing mechanisms and biofilm formation.[73]

Furthermore, coatings can be enhanced by incorporating antimicrobial peptides, antibiotics, bactericidal agents, or metal ions to improve their antibacterial properties.[66,74–76] With the advancement of nanotechnology, researchers have discovered various nano-topographies that possess antibacterial and even bactericidal properties, mimicking natural surfaces like leaves, insect wings, or animal skins.[77–87] Despite extensive exploration of these strategies, in vivo studies are scarce, and their clinical performance has not been adequately tested. In addition, most research has been conducted in vitro, often against selected bacteria, which may not accurately replicate the complex oral microbiological environment. An in vivo study examined the effects of silver nanoparticles,[88] and although it demonstrated that these nanoparticles could effectively prevent biofilm accumulation, their cytotoxicity limits their clinical application. The primary challenges hindering the implementation of these strategies in clinical practice include the complexities of coating design, insufficient or inconsistent antimicrobial efficacy, and safety concerns in human clinical trials.[88]

4.2 | Laser irradiation

Another emerging antimicrobial approach for treating peri-implant diseases is laser irradiation. The term "laser" stands for "light amplification by stimulated emission of radiation," and its application in periodontics was first introduced in the 1990s. Lasers emit single-wavelength light directed into a concentrated beam which, upon interaction with the target tissue, may be scattered, transmitted, absorbed, or reflected (Figure 2). Depending on the energy level and the type of tissue interaction, lasers can produce various effects, including heating, coagulation, or vaporization. Over time, lasers have become valuable tools in diagnostics, surgical procedures, and physiological research.[89] In recent years, laser technology has been applied to decontaminate inflamed peri-implant tissue as an alternative to conventional peri-implant treatments. Compared to other techniques, lasers can cover a broader treatment area and may offer enhanced precision and efficacy in reducing the microbial load.[89] Various types of lasers have been investigated for this application, including the Er:YAG (Erbium-Doped Yttrium Aluminum Garnet) laser (Figure 3), CO_2 lasers, diode lasers, the Er:Cr:YSGG (Erbium, Chromium doped Yttrium Scandium Gallium Garnet) laser, and Nd:YAG (Neodymium-doped Yttrium Aluminum Garnet) lasers.[90] However, within the past decade, only the Er:YAG and diode lasers have consistently appeared in the literature as effective antimicrobial modalities for peri-implantitis treatment. In this review, we will specifically focus on the research published over the last 10 years.

Hauser-Gerspach et al.[91] published an in vitro study in which Er:YAG-irradiated titanium surfaces were tested with bacteria. The Er:YAG laser effectively killed *Porphyromonas gingivalis* and *Streptococcus sanguinis*, and there were no significant differences in cell adhesion compared to untreated samples. These results highlight the desirable antibacterial effects of laser treatment, with no toxic impact on cell adhesion or growth, thus laying the groundwork for its use in this field. Al-Hasedi et al.[92] also confirmed the use of Er:YAG laser as an effective method for surface decontamination, comparing it with conventional approaches such as titanium brushes or plastic curettes. In Figure 2, the different methods can be observed, highlighting how the laser stands out as a bactericidal strategy. In turn, Chen et al.[93] tested the combination of laser with air-powder abrasive treatment, with promising results as an adjunctive tool. Shifting the focus to clinical studies, Er:YAG laser therapy for peri-implantitis was evaluated in 2015 by Schwarz et al.,[94] who compared it against chlorhexidine. The results showed similar efficacy between the two techniques, with significant improvements observed over the short term. This positions Er:YAG laser therapy as a viable alternative to chlorhexidine. Thus, Er:YAG laser therapy emerged as an interesting approach for implant surface detoxification, as no surface modifications were observed. A more recent study published by Wang et al.[36] also supported the use of the Er:YAG laser for the regenerative surgical therapy of peri-implantitis sites, demonstrating positive results in terms of pocket depth and clinical attachment level 6 months after surgery.

As mentioned above, the other type of laser that has been reported for use in peri-implantitis therapy is the diode laser. However, a review of the literature shows that two clinical studies published 10 years ago[95,96] found that the diode laser does not appear to provide additional benefits for peri-implant healing compared to conventional treatments. Nevertheless, more recent clinical studies have shown that diode laser therapy may offer benefits for peri-implant healing, suggesting its potential as a valuable adjunct to conventional treatments. A 2-year clinical study demonstrated the effectiveness of the diode laser as an adjunct to nonsurgical

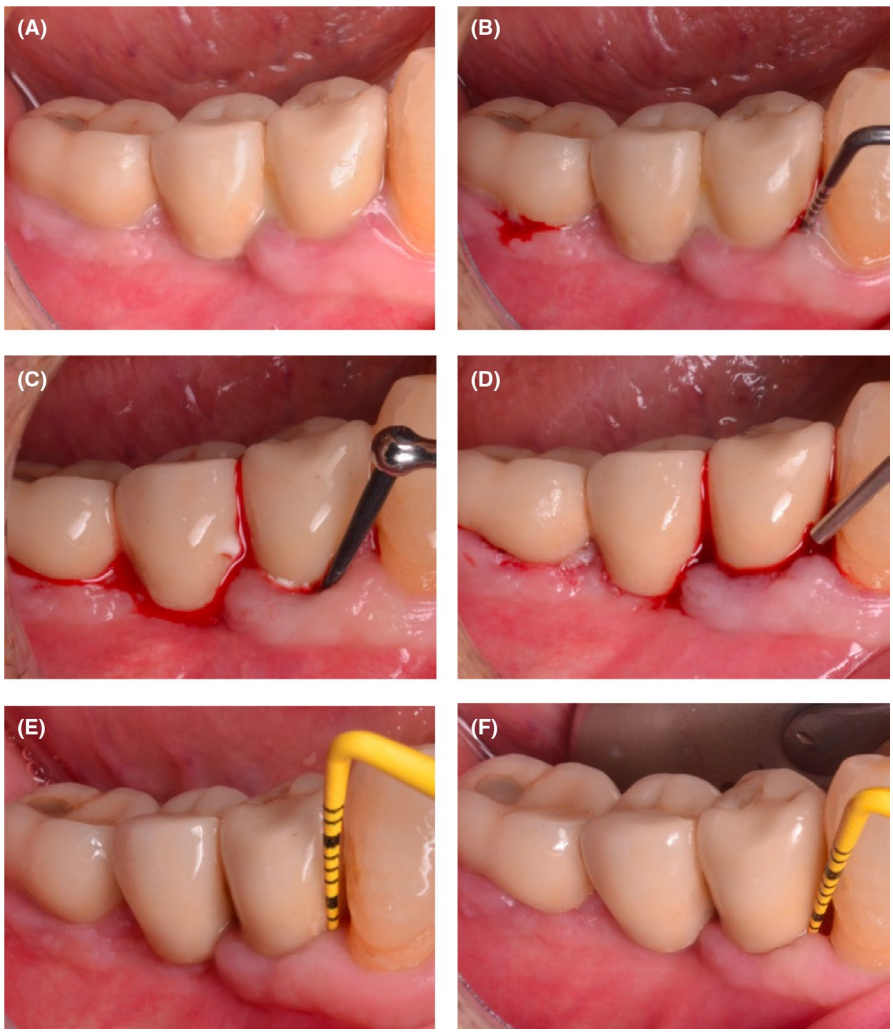

FIGURE 2 Implant diagnosed with peri-implant mucositis (A, B) managed by means of mechanical plaque elimination (C) and diode laser 976 nm set at 10 Hz and 3.75 J energy (D). Re-evaluation during supportive peri-implant care performed at 3-month (E) and 6-month follow-up demonstrated a healthy condition (F).

mechanical therapies.[97] Similarly, more recent studies have shown promising results with diode laser irradiation on peri-implantitis sites, consistently using it as a supportive method alongside conventional treatments.[98,99] On the other hand, Aimetti et al.[100] recorded no statistically significant clinical benefit with the use of the diode laser as compared to nonsurgical mechanical treatment alone in controlling peri-implant mucositis at 3 months. Likewise, Roccuzzo et al.[101] found that repeated adjunctive application of the diode laser in the nonsurgical management of peri-implantitis failed to afford significant benefits compared with mechanical instrumentation alone.

Thus, the literature suggests that Er:YAG laser therapy is a promising standalone technique for peri-implant diseases, while the diode laser seems to be effective primarily as a supportive tool in conjunction with mechanical methods.

4.3 | Metal ions and nanoparticles

Metal cations (Me^{n+}) and metallic nanoparticles (Me-NPs) have been widely investigated for their antimicrobial properties.[102] The Me^{n+} claimed to have antimicrobial activity and which have been widely studied as metal-free agents or as nanoparticles include silver (Ag), gold (Au), zinc (Zn), and copper (Cu), as well as some metal oxides such as ZnO, CuO, MgO, ZnO_2, Cu_2O, and TiO_2. Despite generalized concern about the potential toxicity of locally delivered Me^{n+} and Me-NPs, the effect of metals differs between bacterial and mammalian targets due to their different metal transport systems and metalloproteins.[103] Me-NPs have been investigated for the control of peri-implant diseases as preventive agents incorporated on the surface of dental implants and abutments, and delivered during treatment of the disease.

With regard to the underlying mechanism of action, it has been reported that Me^{n+} or Me-NPs are released from the modified surfaces or are delivered locally, and are electrostatically attracted to the bacterial membranes, where a series of potential events may occur: (1) impairment of cell membrane function or nutrient assimilation; (2) formation of reactive oxygen species (ROS) with consequent damage to lipids, proteins, and DNA through oxidative stress; (3) damage to the plasma membrane, resulting in the leakage of cell contents; and (4) direct interference with both proteins and DNA, impairing their function and disturbing cellular metabolism

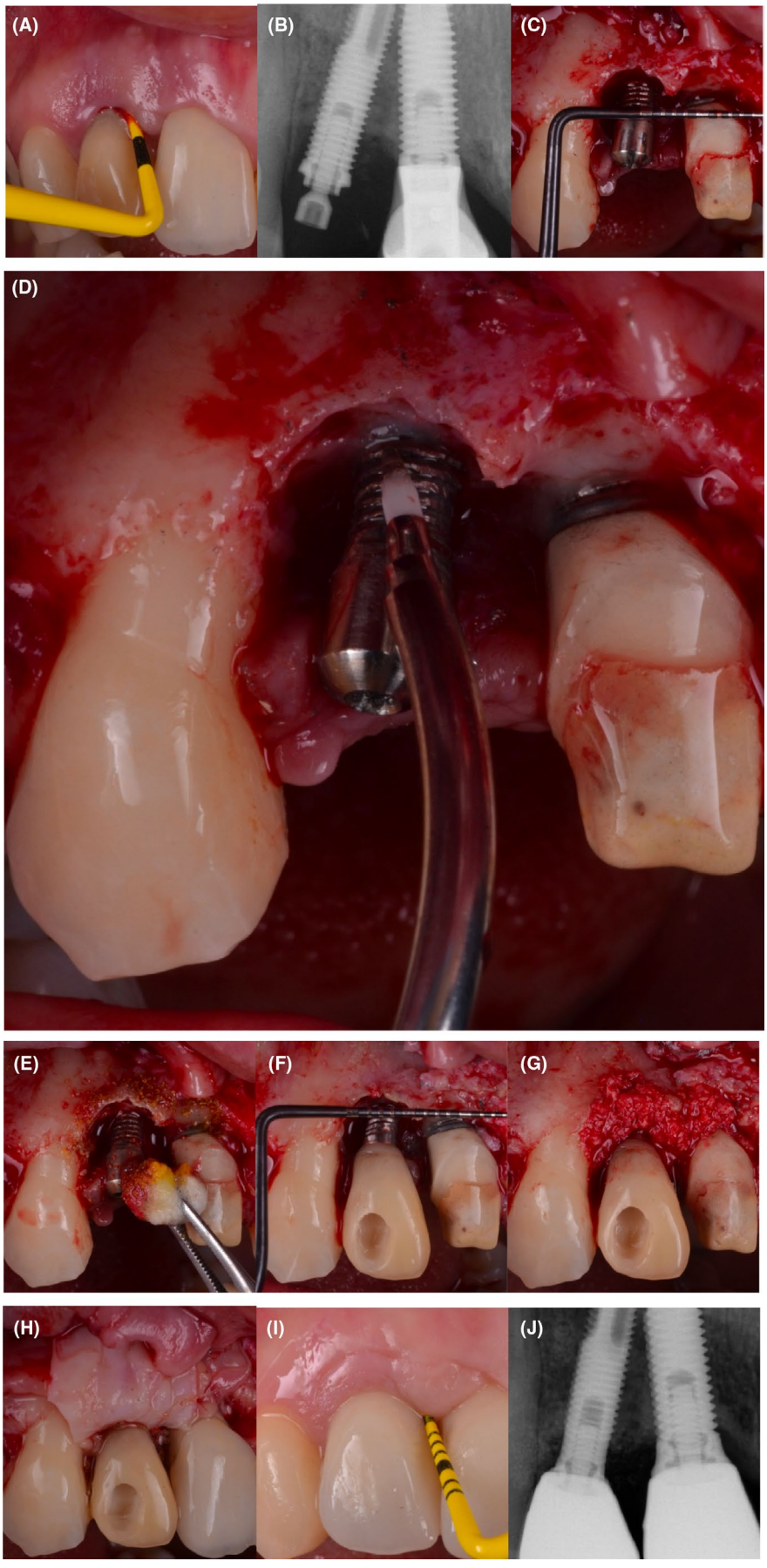

FIGURE 3 Peri-implantitis-related bone defect treated by means of reconstructive therapy; (A) clinical diagnosis of peri-implantitis, (B) radiographic evidence of bone loss in a malpositioned implant, (C) combined defect configuration, (D) Er-YAG laser for surface decontamination, (E) pharmacological decontamination using tetracycline chlorhydrate, (F) implantoplasty for the supracrestal component, (G) bone grafting material composed of xenograft and autogenous bone, (H) de-epithelialized connective tissue graft, (I) clinical outcome at 3-year follow-up demonstrates peri-implant healthy conditions, and (J) radiographic evidence of bone gain.

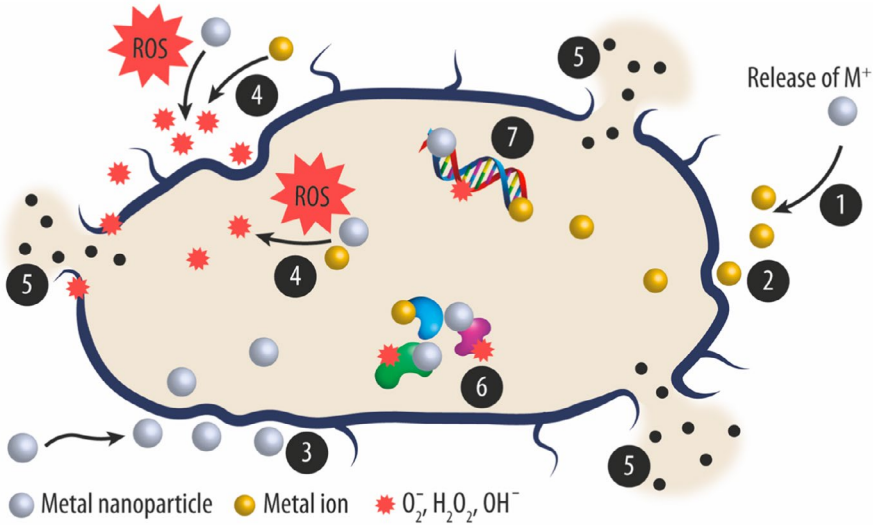

FIGURE 4 Antibacterial mechanisms of metal ions and nanoparticles. The central mechanisms of action are as follows: (1) release of metal ions from the metal nanoparticles; and (2) direct interaction of the metal ions and/or (3) metal nanoparticles with the cell wall through electrostatic interactions, leading to impaired membrane function and nutrient assimilation; (4) formation of extracellular and intracellular reactive oxygen species (ROS), and damage to lipids, proteins, and DNA through oxidative stress; (5) high levels of metal binding to the cell envelope and high ROS levels can cause damage to the plasma membrane and thus lead to leakage of the cell contents; (6, 7) upon metal uptake, metal nanoparticles and metal ions can directly interfere with both proteins and DNA, impairing their function and disturbing cellular metabolism, in addition to metal-mediated ROS production. Reproduced with permission from Godoy-Gallardo et al.[102]

(Figure 4). Other types of nonmetallic nanoparticles, such as quaternary ammonium polyethyleneimine, chitosan, and silica nanoparticles have also demonstrated potential for controlling biofilms.[104] Vargas-Reus et al.[105] found the antimicrobial activity of a series of nanoparticles against *Prevotella intermedia*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* to be as follows, in descending order: Ag > Ag + CuO > Cu2O > CuO > Ag + ZnO > ZnO > TiO2 > WO3. In that same study, time-kill assays revealed that ZnO-NP produced a significant decrease in growth of all species tested within 4 h, reaching 100% within 2 h for *Porphyromonas gingivalis* and within 3 h for *Fusobacterium nucleatum* and *Prevotella intermedia*.

Se-NPs have also been proposed as antimicrobial agents for the treatment of peri-implant diseases, with notable potency against *Porphyromonas gingivalis*. Relevantly, Se-NPs also induced osteoblastic differentiation, with a range of Se-NP concentrations showing multifunctional properties that may contribute to re-osseointegration following treatment.[106] MgO-NPs have shown activity against a large series of oral bacterial strains, though greater concentrations of MgO-NPs were needed to effectively inhibit bacterial growth—with the exception of *Actinomyces israelii*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Staphylococcus aureus*, *Streptococcus mutans*, and *Streptococcus sobrinus*.[107]

Many different treatments and coatings incorporating Me^{n+} and Me-NPs have also been investigated in vitro.[108] These agents can be implanted in treated dental implants and then exert contact-killing and/or mid-range killing effects when released from the surface. Effective examples with embedded Ag, Cu, and ZnO have been reported.[109] A novel ZnCuO-NP coating for dental implants has demonstrated potency against a multispecies biofilm composed of *Streptococcus sanguinis*, *Actinomyces naeslundii*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum* that was grown for 14 days. The coating was stable and cytocompatible with osteoblasts and macrophages. Coatings and treatments with Ag and Ag-NP are widely studied materials for the control of peri-implantitis and other dental material-related infections.[102] However, because of limited potency unless high concentrations of Ag are used, or due to cytotoxicity concerns, Ag and Ag-NPs have been modified and/or combined with other agents. For instance, Ye et al.[110] combined Ag-NPs with antimicrobial peptides in a coating on Ti surfaces with synergistic antimicrobial effects in vitro and in vivo. The improved activity of the coating was attributed to the combination of bacteria contact-killing properties of the antimicrobial peptides with mid-range bacteria killing ability of the released Ag-NPs. Another way to improve the anti-infective activity of NPs is by using stabilizers that coat the NPs and provide them with a "Trojan horse" effect to allow their uptake in a specific subset of bacterial cells. An example of this is the study by Frober et al.[111] who coated ZnO-NPs with glucose-1-phosphate to target gram-negative strains.

Despite the great progress made over the last decade in the investigation of Me^{n+} and Me-NPs as effective agents for controlling peri-implantitis, clinical studies using them are scarce. This is in contrast to orthopedic implants with incorporated metal ions, which are already found on the market and are used by surgeons around the world.[112] The controlled release of metal-based antimicrobials in order to avoid toxicity and other side effects, as well as the broadening of their application to other devices and implants, remains a challenge, particularly in relation to dental implants.

4.4 | Pulse electromagnetic fields

Pulse electromagnetic field (PEMF) application as an adjunct to other measures or as a therapeutic modality in itself has been demonstrated to accelerate fracture repair by acting upon cell proliferation and differentiation through a series of metabolic pathways.[113] In bone healing, PEMFs have been shown to act upon osteoprogenitor cells, seeking to achieve the forming of bone stimulated by a demineralized bone matrix.[114] This technique has been further noticed to increase the activity of kinases involved in the intracellular signaling pathways, modulating antiinflammatory effects to increase the quantity of adenosine A2A receptors and upregulating bone morphogenetic protein (BMP)-2.[115] Moreover, it was demonstrated that PEMFs increase the osteogenic commitment of mesenchymal stem cells via the mTOR pathway under TNF-α mediated inflammatory conditions. In addition, it was shown that PEMFs increase the expression of IL-10 (an antiinflammatory cytokine) and reduce the expression of IL-1 (a proinflammatory cytokine).[116] These data suggest the potential contribution of PEMFs in achieving (re)osseointegration, and thus in treating peri-implantitis to enhance cell recruitment and bone repair. In turn, PEMFs have also been confirmed to reduce the activity of osteoclasts via macrophage-derived exosomes.[117] This would assist in limiting disease progression in the case of peri-implant biological complications (Figure 5).

On the other hand, PEMFs have been demonstrated in vitro in a subgingival biofilm model to induce antimicrobial effects. Specifically, after 96 h, the mean levels of *Eubacterium nodatum*, *Fusobacterium nucleatum* subspecies (ssp) *nucleatum*, *Streptococcus intermedius*, *Streptococcus anginosus*, *Streptococcus mutans*, *Fusobacterium nucleatum* ssp. *Vicentii*, and *Capnocytophaga ochracea* were increased at sites not exposed to PEMFs compared to implants exposed to magnetic fields.[118] In this sense, a randomized controlled trial testing the effectiveness of nonsurgical treatment for the management of peri-implantitis using PEMFs as an adjunctive measure for 30 days recorded greater bone defect fill at 3 months and a decrease in the levels of IL-1 at 2 weeks following mechanical debridement.[119] Accordingly, despite the potential of PEMFs as an emerging antimicrobial strategy (Figure 6), more long-term trials are needed to test their efficacy compared to traditional measures for the management of peri-implantitis.

4.5 | Argon plasma

When a gas is ionized, it transitions into a state known as physical plasma. At atmospheric pressure, plasma remains electrically neutral, comprising a complex mixture of ions, electrons, vacuum ultraviolet (VUV) and ultraviolet (UV) radiation, short-lived free radicals, and chemically reactive neutral species, and it also generates heat.[120] The application of plasma has been widely used in numerous fields due to its unique electrical, optical, thermal, chemical, and physical properties.[121] Recently, this technology has drawn increased attention for its potential applications in the medical field, attributed to its tissue-compatible temperatures (in the case of atmospheric plasma) and the generation of reactive species, which have been shown to positively influence cellular responses in various contexts.[122] Additionally, plasma treatment has been investigated for its ability to reduce bacterial attachment and biofilm formation, with promising results observed in both in vivo studies and in clinical trials.[123]

In implant dentistry, several applications of plasma technology have been explored and implemented. Plasma can influence a wide variety of material surface functional properties such as wettability, free energy, adhesion/cohesion, refractive index, hardness, chemical inertness, lubricity, and general material surface biocompatibility. These functional effects arise from surface changes that include the elimination of organic surface contaminants (i.e., sterilization or sanitization), ablation of the most superficial layers (resulting in topography/roughness changes to enhance mucosal sealing), crosslinking or branching of surface molecules (typically occurring with polymers), and modification of the surface chemical composition or deposition of chemical moieties.[124] Consequently, plasma is an attractive method for dental implant surface modification, particularly for the prevention of peri-implantitis.

The antimicrobial effects of plasma treatment are largely driven by the generation of reactive species, including free radicals, which target various bacterial components. These species can compromise the integrity of bacterial cell walls and membranes by inducing strong electrostatic disruptions. Furthermore, reactive oxygen and nitrogen species facilitate the oxidation of essential bacterial molecules, including lipids, proteins, polysaccharides, and nucleic acids. In this field of research, a preliminary study by Koban et al.[122] compared chlorhexidine to the efficacy of nonthermal argon plasma on titanium discs. This type of in vitro study explores the application of atmospheric pressure plasma treatment on implant-based material surfaces following biofilm growth. Koban et al.[122] found that plasma treatment applied to biofilm resulted in superior antimicrobial effects compared to chlorhexidine. The study also compared several atmospheric plasma devices, all of which showed high antibacterial efficacy. Several studies have likewise employed plasma treatment as a decontaminant method for surfaces infected with various bacteria.[123,125] The literature indicates that plasma treatment is highly effective against several bacterial strains, such as *Streptococcus mitis*[126] and *Porphyromonas gingivalis*,[127] in mono-species biofilms. Additionally, this treatment is effective against multi-species biofilms.[128,129] For instance, Panariello et al.[128] used low-temperature argon plasma to treat multi-species biofilms formed by *Actinomyces naeslundii*, *Porphyromonas gingivalis*, *Streptococcus oralis*, and *Veillonella dispar* after 24 h, 3 days, and 7 days of growth, recording a significant reduction in bacterial growth under all conditions compared to the controls. However, despite the effectiveness of plasma treatment against bacterial growth, *Streptococcus aureus* appears to develop tolerance to it in both mono-species and multi-species biofilms with *Candida albicans* and *Pseudomonas aeruginosa*, where the latter two strains show reduced growth.[130] In a more recent study, Lee et al.[125] demonstrated lower bacterial viability in comparison to the controls in nonatmospheric pressure argon plasma-treated samples cultured with oral microcosm biofilm derived from human

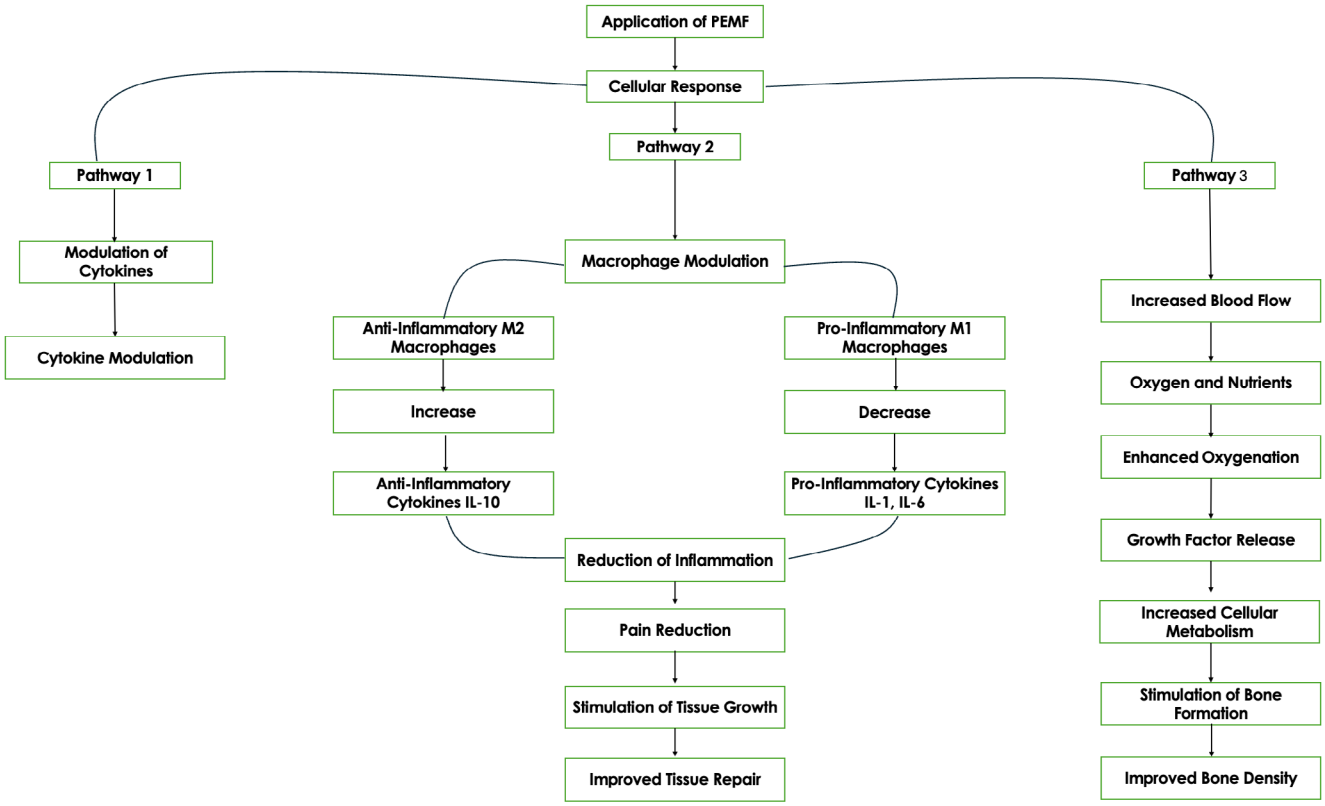

FIGURE 5 The diagram illustrates how pulse electromagnetic fields work in regenerative therapy. Application of PEMF: Therapy begins with the application of pulsed electromagnetic fields to the treatment area. Cellular response: This triggers an immediate cellular response in the targeted tissues. Three main pathways: The cellular response activates three primary pathways: (A) Cytokine modulation: PEMF therapy increases antiinflammatory cytokines and decreases proinflammatory cytokines. This leads to a reduction in inflammation; (B) Blood flow: The therapy enhances blood flow, increasing oxygen and nutrient delivery to the tissues. This results in enhanced tissue oxygenation and increased cellular metabolism; (C) Macrophage regulation: PEMF increases antiinflammatory M2 macrophages and decreases proinflammatory M1 macrophages, further contributing to inflammation reduction and promoting tissue repair. Intermediate effects: These pathways lead to several beneficial effects: pain reduction, enhanced cellular metabolism, promotion of wound healing, and increased growth factor release. Tissue-specific outcomes: Soft tissue regeneration, improved gingival health, stimulation of bone formation, enhanced osseointegration of dental implants. Final outcomes: Ultimately, these mechanisms contribute to improved patient comfort and better overall treatment outcomes in dental procedures.

saliva on hydroxyapatite discs. Additionally, plasma treatment has been studied in combination with other techniques for antimicrobial preventive action.[131,132] Combining plasma treatment with mechanical treatments and cleaning procedures has also been a focus of research. For example, brushing surfaces before plasma treatment effectively removes preexisting biofilm from subgingival plaque and promotes cell growth.[131] Similarly, using a water jet or air polishing is equally efficient in biofilm removal and in preventing regrowth compared to controls.[132]

The studies to date have primarily focused on the use of plasma devices for decontamination processes (Table 3). However, some research has explored the pre-treatment of samples before the incubation of cells or bacteria.[133] Plasma treatment of implant-based material surfaces has been shown to enhance cell adhesion and spreading by improving important surface characteristics such as wettability, functional protein configuration, and the creation of biofunctional groups on the surface.[133] Pan et al. observed improved proliferation of osteoblast-like cells and enhanced osteoblastic differentiation on plasma-treated surfaces while also confirming the antibacterial effects of the treatment. Notably, *Porphyromonas gingivalis* exhibited a significant reduction in adhesion and growth in these studies.[133]

Another relevant area of research is the potential of plasma treatment to aid in controlling peri-implantitis beyond its antibacterial effects. Plasma treatment of implant surfaces not only prevents bacterial adhesion and growth but also increases cell adhesion, thereby creating an optimal environment for proper implant integration. Canullo et al. conducted a clinical trial in which plasma pre-treated healing abutments were implanted in patients to assess the effects of plasma treatment on various micro-topography designs at 2 months post-implantation.[135] The results showed lesser bleeding on probing and a reduced plaque index in the plasma pre-treated group, indicating less advanced plaque formation. This is in line with findings from the same group demonstrating that abutments treated with plasma assisted in reducing plaque accumulation and inflammation, with the stimulation of collagen and soft tissue, but without effects on the epithelial tissues or keratinization[137] (Figure 7). Alsahhaf et al. published a 5-year follow-up study comparing the use of argon plasma disinfection prior to prosthetic loading versus

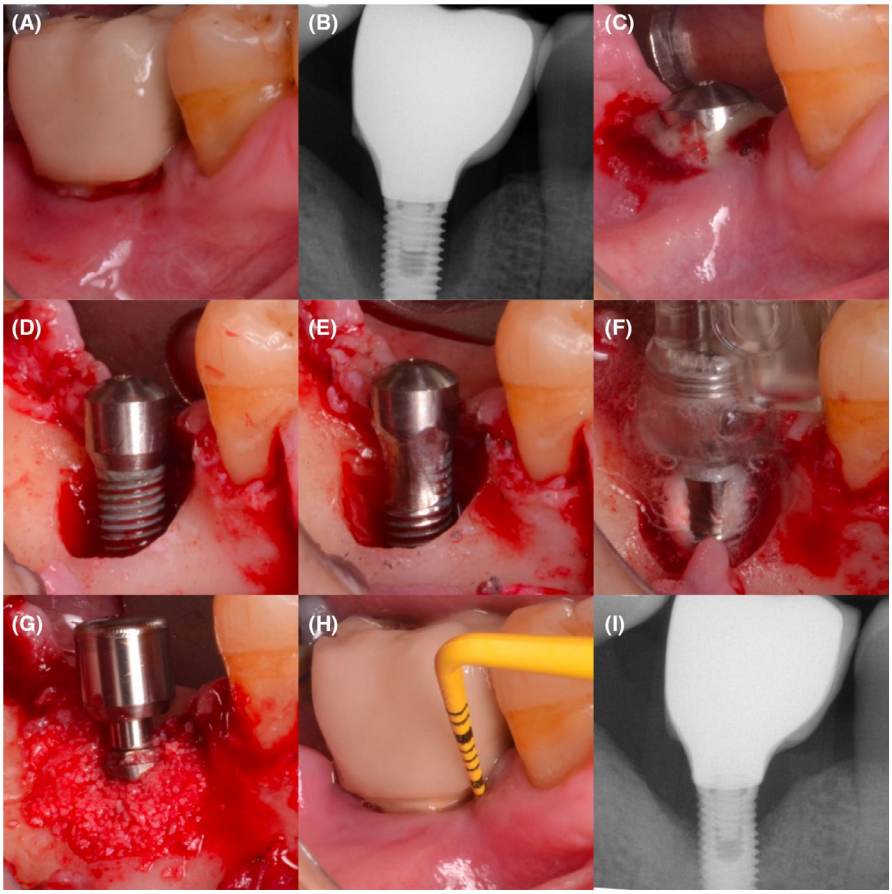

FIGURE 6 Pulse electromagnetic fields used as adjunctive measure to surgical reconstructive therapy of peri-implantitis. (A) Clinical diagnosis of peri-implantitis; (B) advanced peri-implantitis-related bone defect; (C) persistent disease following nonsurgical therapy; (D) bone defect after curettage of the granulation tissue; (E) implantoplasty at the area outside the bony housing; (F) electrolytic surface decontamination modality for the intrabony component; (G) bone grafting and PEMF abutment placed for 3 weeks; (H) 9-month follow-up examination suggesting disease resolution; (I) radiographic bone fill during follow-up.

0.2% chlorhexidine gel. The study yielded promising results, finding no significant differences between the groups, and thereby demonstrating that argon plasma treatment is comparable to 0.2% chlorhexidine treatment. Thus, plasma technologies have potential for preventing and treating peri-implantitis, though further studies are needed beyond in vitro assessments of the removal and/or prevention of biofilm growth on dental implant surfaces.[136]

4.6 | Biomolecular coatings

Antibiotic-based coatings are currently in disfavor due to their limited success in preventing biofilm formation and also because of the increasing global concern about antimicrobial resistance, the so-called "*climate change of health*," since it threatens our worldwide health care systems on a daily basis.[138] Thus, we need novel solutions that provide alternatives to the use of antibiotics. In this context, coatings on dental implants composed of biomolecules with known specific activities and, in particular, with antimicrobial properties, have emerged as one of the most extensively explored strategies for preventing bacterial colonization and thus peri-implant infections, with a minimized risk of bacterial resistance. In this regard, the mechanism of action of these coatings is based on biomolecule-bacterial membrane interactions that disrupt the bacterial envelope, thus making it significantly more difficult for bacteria to develop resistance to these agents than to antibiotics.[139] Proteins, peptides, and carbohydrates constitute a biomolecular toolbox that enables biologically specific, robust, and chemically versatile technologies to provide control over the activity of the modified implant surfaces.[140]

This has been one of the most prevalent lines of research, at least in vitro, for addressing peri-implantitis, and in this regard several comprehensive and up to date reviews on the topic can be found in the literature.[141] An exhaustive exploration of the literature reveals that, beyond differences in biomolecular composition, there are two main types of biomolecular antimicrobial coatings for preventing biofilm development, namely coatings that kill bacteria by contact and coatings that release the antimicrobial agent and can also kill bacteria in the mid-range from the protected surface. Combinations of these two approaches have also been explored. From this body of published studies, we will comment on the contributions that have led the way in the field and have resulted in sound coatings with an increased potential for translation into the clinical setting.

A wide range of antimicrobial peptides (AMPs) have been explored as coatings for preventing peri-implantitis.[142] AMP coatings offer broad spectrum and rapid antimicrobial behavior, low toxicity, and, as already mentioned, a lesser risk of antimicrobial resistance.[142] All together, this makes AMPs ideal therapeutic agents for implant coatings.

GL13K and its D-enantiomer, D-GL13K peptide, are well-characterized AMPs widely used for coating dental implants. These are self-assembling, cationic, amphipathic designer AMPs derived from the salivary protein BPIFA2.[143] Initial work with GL13K established that these peptides could be anchored on titanium and reduce

TABLE 3 Summary of argon plasma application to treat and prevent peri-implant diseases.

Author	Study type	Plasma device	Surface treated	Study control and variables	Effects of plasma on peri-implant disease
Koban et al.[122]	In vitro	Plasma jet Argon (kINPen 09, 5 slm gas flow, 7 mm) Dielectric barrier discharge (37.6 Hz, 8.4 kV, 1 slm) Volume dielectric barrier discharge (15 mm, 0.05 slm, 40 kHz, 10 kV)	Titanium discs (machined)	Antibacterial effects (*S. mutans* and saliva biofilm) C: Antiseptic treatment (chlorhexidine digluconate (CHX)) and NaCl solution	*S. mutans*: VDBD significantly higher reduction factor (RF) than CHX. Saliva biofilm: significantly greater antimicrobial effects in the three plasma configurations compared to CHX.
Duske et al.[131]	In vitro	Nonthermal atmospheric pressure Argon plasma-Oxygen (kINPen08, 2–3 W, 1.82 MHz, 2–6 kV, 5 mm)	Titanium discs (grade IV, sandblasted-etched)	Human osteoblastic cell growth, cell morphology, cell area and number. Biofilm regrowth and cell growth.C: No C: No C: No plasma-treated samples	Plasma treatment on biofilm-covered discs resulted in recovery of osteoblast growth before biofilm culture
Preissner et al.[126]	In vitro	Plasma jet Argon (Kkinpen MED, 4.3 bar/argon gas flow 4.3 slm, 60 sec)	Titanium dental implants (sandblasted and acid-etched hydrophilic microrough surface, 0,5 mm machine collar, external hexagon)	Antibacterial effects (*S. mitis*) C: diode laser (DL).	Plasma treatment on biofilm-covered discs resulted in higher bactericidal efficacy compared to control implants
Canullo et al.[134]	In vitro	Atmospheric pressure dielectric barrier discharge Argon (8 W, 2 mm, 2 min)	Titanium discs (grade IV, MAC-TPS - ZRT)	WCA. Bacterial adhesion. Protein adsorption. Cell adhesion, morphology and viability.C: No C: No C: No plasma-treated samples	Plasma treatment reduced bacterial growth but did not enhance osteoblast proliferation. Enhanced protein adsorption (TPS-ZRT)
Carreiro et al.[127]	In vitro	Low-temperature plasma jet (Kinpen, 8 W at 220 V, 50/60Hzm argon flow 5 slm)	Titanium grade 4 discs (sandblasted and acid-etched, 6 mm diameter, 2 mm thickness, 0,8505 ± 0,128 μm roughness)	Antibacterial effects (*P. gingivalis*). C: CHX solution for 1 min	Reduction of biofilm on Ti discs after plasma treatment.
Pan et al.[133]	In vitro	Plasma reactor - Glow discharge plasma (Ar-GDP, 85 W, 13.56 MHz, 100 mTorr, 15 min)	Zirconia discs (10 mm diameter, 1 mm thickness)	Antibacterial effects (*P. gingivalis*) C: Nontreated Zr discs	Significant reduction of adhesion and growth of *P. gingivalis* in treated Zr discs.
Panariello et al.[128]	In vitro	Low-temperature plasma jet (kINpen, 1–3-5 min, 3–10 mm distance)	Titanium discs (7.5 mm diameter, 2 mm thickness)	Antibacterial effects (multispecies biofilm: *A. naeslundii*, *P. gingivalis*, *S. oralis*, *V. dispar*) C: Amoxicillin, metronidazole and chlorhexidine treated samples and nontreated samples	Plasma treatment significantly reduced all bacterial species compared to nontreated samples.
Matthes et al.[132]	In vitro	Cold atmospheric plasma jet (perilINPlas, INP, 0.95 MHz at 2-3kVpp, 1.6 W)	Titanium implants (Ankylos, C/X Implant A9.5, Ø3.5, L9.5) and Titanium discs (diameter 5 mm, thickness 1 mm, Ra = 1.23 μm, Rq = 1.53 μm)	Biofilm removal by plasma treatment in combination with WaterJet. C: Sand-blasted, acid-etched, sterilized samples	Combination of WaterJet and cold-atmospheric plasma treatment potently removed biofilm from titanium surfaces
Florke et al.[129]	In vitro	Cold atmospheric plasma jet (kINpen, 5 W)	Titanium implants (TiPure Plus BEGO Semados SC, 3.75 × 8.5 mm)	Decontamination. C: noninfected implants, nontreated infected implants	No total bacteria decontamination achieved

TABLE 3 (Continued)

Author	Study type	Plasma device	Surface treated	Study control and variables	Effects of plasma on peri-implant disease
Canullo et al.[135]	*Clinical study*	Argon plasma reactor (Diener Electronic, GmbH, 75 W, 10 MPa, 12 min)	Healing abutments with two different microtopographies: smooth surface (MACHINED) and rough ultrathin threaded microsurface (ROUGH)	Antibacterial effects. C: nontreated abutments	Plasma pre-treatment contributed to less advanced biofilm accumulation
Baz et al.[130]	In vitro	Cold atmospheric plasma jet (25.5KHz, 6 slm, 8 kV p-p)	Multispecies biofilm hydrogel matrix	Killing bacteria effects.	Depending on the biofilm, morphological effects could be obtained after plasma treatment
Lee et al.[125]	In vitro	Nonthermal atmospheric pressure plasma (Plasma Pipete®, 4 W, 10 kV, 100 kHz, 0,02 MPa, 5 min)	Oral microcosm biofilms growth in hydroxyapatite disks	Antibacterial effects. C: chlorhexidine, nontreated samples	Viability of bacteria reduced on plasma-treated samples. Number of bacteria lower in chlorhexidine control.
Alsahhaf et al.[136]	*5-year follow-up clinical trial*	Plasma reactor (Diener Electronic, 75 W, room temperature, -10 MPa, 12 min)	Patient abutments	Crestal bone loss, Plaque index, Probing depth. C: chlorhexidine, steam-disinfection	No differences between groups. Plasma disinfection can be compared to gold standard method chlorhexidine

the load of *Porphyromonas gingivalis*.[144] Subsequent work showed similar antimicrobial activity against an early colonizer, *Streptococcus gordonii*[145] and microcosm biofilms,[146] without affecting osseointegration in a rabbit model. More recent work has shown the antimicrobial behavior of GL13K, in vitro and in vivo, to be dependent on the formation of twisted nanoribbon structures triggered by the neutralization of cationic side groups before surface anchoring.[147] The coatings with GL13K are very stable and resist degradation under simulated biofunctional scenarios, which has been attributed to the high hydrophobicity of the GL13K peptide coatings.[148] As detailed in other sections of this review, GL13K peptide coatings also have immunomodulatory functions and have been combined with silver nanoparticles, showing relevant synergistic effects in preventing infection in in vivo experiments.[149] Finally, GL13K peptides have also been combined with other biomolecules to impart multifunctionality to dental implant surfaces.[150] Other peptides, such as LL-37, hlf1-11, HBD-3, melamine, members of the Tet family, and chimeric peptides have also been investigated as coatings on titanium surfaces for dental implant applications.[140]

Antimicrobial proteins have also been investigated as coatings for preventing peri-implantitis. Lactoferrin was adsorbed on titanium, showing effectiveness in preventing the formation of biofilms of *Streptococcus gordonii*. Gelatin, collagen, and silk fibroin have also been used as protein coatings with the ultimate goal of preventing implant infections,[151] even though these molecules do not have intrinsic antimicrobial properties. In this case, the strategy is to favor mammalian tissue-regenerative cell colonization over bacterial colonization, that is, increasing the involvement of osteoblasts, fibroblasts, etc., to "*win the race for the surface*."[152] In some cases, these proteins are combined with AMPs to enhance their infection-preventive properties.[153] Chitosan, a well-known multifunctional antimicrobial biopolymer, and other carbohydrates and glycosaminoglycans have been explored as coatings for preventing the bacterial colonization of titanium dental implants.[151] Apart from its valuable antimicrobial properties, affordability, and biodegradability, chitosan has been used quite broadly for coating dental implants due to its cationic nature, which makes it amenable for strong electrochemical interactions with the metallic substrate and as a component of multifunctional layer-by-layer coatings in combination with polyanions,[154] highly anionic proteins, and glycosaminoglycans, such as hyaluronic acid.[155] Chitosan has also been combined with AMPs in composite coatings. For instance, Xu et al. formulated a carboxymethyl chitosan and peptide-decorated polyetheretherketone ternary biocomposite coating with enhanced antibacterial activity and improved osseointegration,[156] and Palla-Rubio et al. combined chitosan with silica particles stabilized with three different alkoxysilanes to obtain biodegradable hybrid coatings with potency against a gram-negative strain.[157] Finally, alginate, a very widely available and very cheap carbohydrate, has also been used in composites co-doped with lanthanum and silicon hydroxyapatite to produce coatings with antimicrobial and bone regenerative properties.[158]

Most of the studies on the use of biomolecules as antimicrobial coating materials to prevent peri-implantitis have reported

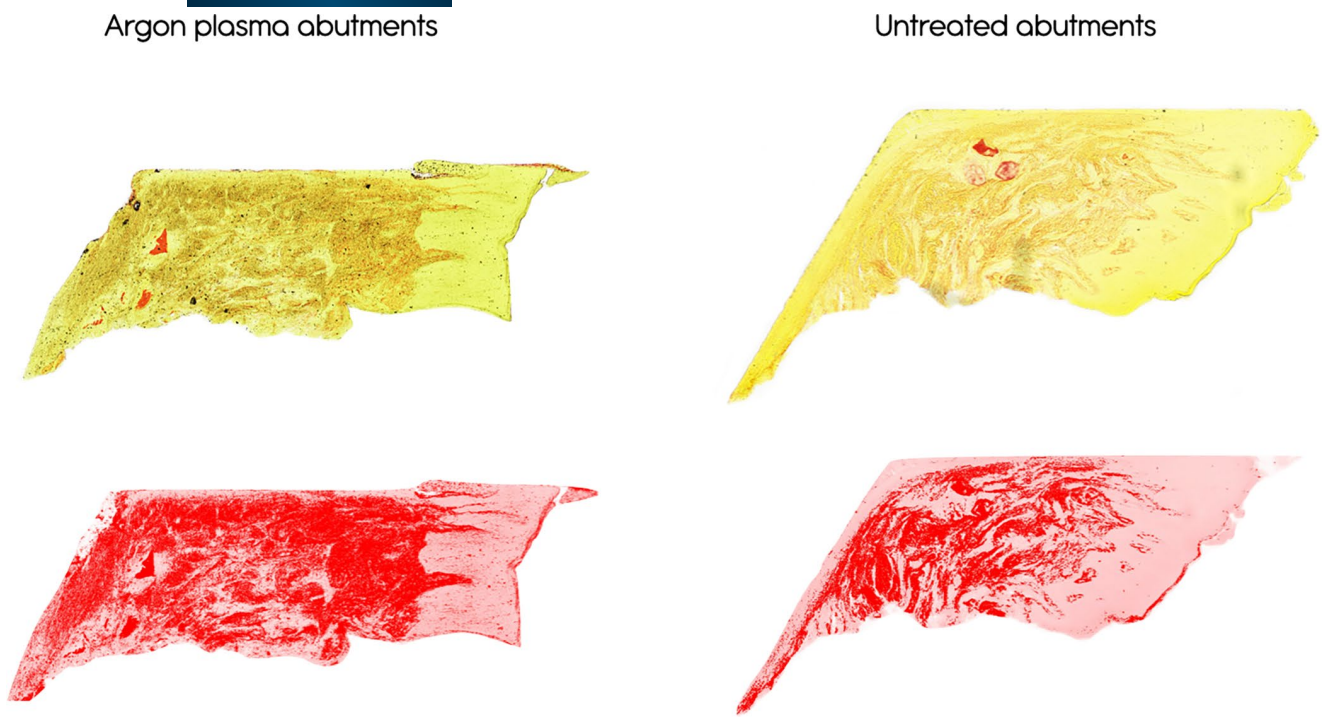

FIGURE 7 Images relating to collagen staining using Sirius red. Untreated sample, treated sample; images processed with ImageJ using color deconvolution to isolate the red-colored collagen from the yellow-colored background for collagen quantification. Requested with permission from Canullo et al.[137]

promising findings, but these have only been confirmed in in vitro studies. Their in vivo long-term effectiveness has not been successfully demonstrated in any case. Harnessing the full potential of the biomolecular toolkit to develop more effective, off-the-shelf materials and interfaces to address peri-implantitis still needs to be accomplished and requires multidisciplinary synergistic collaborations between academia, health practitioners, the industrial sector, and regulatory agencies.

5 | EMERGING LOCALLY DELIVERED IMMUNOMODULATORY APPROACHES FOR THE PREVENTION AND TREATMENT OF PERI-IMPLANT DISEASES

Peri-implantitis can be prevented and treated using a range of strategies. So far, this review has primarily addressed antimicrobial approaches aimed at preventing bacterial colonization through antibacterial treatments, which have proven effective in mitigating this issue. However, another modern approach for controlling peri-implant infection involves the addressing of chronic inflammation, which can lead to the formation of peri-implant pockets - an environment that facilitates bacterial colonization and the onset of infection. As the role of macrophages and the immunological cascade of events cannot be ignored as a valuable strategy for controlling peri-implantitis, most of the preventive and therapeutic strategies in this field have focused on inducing the polarization of macrophages to an M2 phenotype.[159] M1-like macrophages are "pro-inflammatory," whereas M2-like macrophages are "pro-regenerative," although it is well known that a continuum of macrophage phenotypes is always present.[160] Indeed, surface modification with different biomolecules can influence macrophage polarization.

In 2020, Liu et al.[3] proposed a strategy to create localized immune microenvironments tailored to the implant site. This strategy involved analyzing the environment surrounding the implant to preemptively inhibit key signaling cascades that could negatively impact soft tissue and metal integration. To achieve this, they developed an IL-4 coating for dental implants to target specific immunological pathways, aiming to modulate immune responses and promote successful biointegration. Boda et al. further advanced this concept by combining immunomodulatory strategies with cell-adhesion techniques. They used a hemidesmosome-promoting peptide alongside a polyunsaturated omega-6 fatty acid to modulate the immune response of cells.[150] This method focused on regenerating the epithelium-implant interface to establish stable implant integration, thereby reducing the risk of peri-implantitis-related complications. These recent developments highlight the potential of localized immunomodulatory strategies to enhance implant integration and reduce inflammation-associated complications. Building on this, immunomodulatory peptides emerge as particularly promising molecules for further study, especially in the context of peri-implantitis prevention and treatment. As mentioned earlier, peptides offer significant advantages for biomaterials by improving biocompatibility, degradation, and accessibility. Nonetheless, research on their application in peri-implantitis, especially as coatings, remains limited (Table 4).

TABLE 4 Summary of immunomodulatory approaches to treat peri-implant diseases.

Author	Study type	Treatment approach	Objective	Observations
Chávez-Galan et al.[160]	Review	—	Understanding of macrophage polarization: more than M1–M2 profiles	Potential for targeting specific macrophage subpopulations in therapeutic strategies
Zhou et al.[161]	In vitro	Multifunctional antimicrobial and immunomodulatory peptide coating	GL13K-coated titanium surfaces to immune modulate cell response	GL13K apart from antimicrobial properties, showed immunomodulatory effects on RAW264.7 by reducing proinflammatory cytokine release
Bai et al.[162]	In vitro	Immunomodulatory peptide coating	Osteogenic growth peptide (OGP)-coated titanium surfaces to create an immune microenvironment that enhance osseointegration	Enhanced bone-implant contact, suppressed osteoclast activity, and promoted bone formation by inhibiting the NF-κB signaling pathway, supporting improved bone regeneration under inflammatory conditions
Boda et al.[150]	In vitro	Immunomodulatory peptide and biomolecule coating	Dual keratinocyte-adhesive peptide and antiinflammatory biomolecule coating on titanium	CLA coating suppressed the production of inducible nitric oxide synthase, a proinflammatory M1 marker expressed in LPS-stimulated murine macrophages and elevated expression of anti-CD206, associated to an antiinflammatory M2 macrophage phenotype
Zhuo et al.[163]	In vitro	Multifunctional antimicrobial and immunomodulatory peptide	KR-12-3 peptide tested in solution with bacteria and cells presents antibacterial and immunomodulatory effects	LL-37 derived peptide exhibited both immunomodulatory and antibacterial effects on S. gordonii and LPS-stimulated RAW264.8 cells
Guo et al.[164]	In vitro	Immunomodulatory peptide coating	DOPA-RGD peptide-coated to titanium surfaces to reverse the inflammatory microenvironment	DOPA-RGD peptide coating reduced peri-implant inflammation and promoted M2 macrophage polarization by interacting with integrins α2β1 and αvβ3. The coating also enhanced osteoblast adhesion and osteogenesis, even under inflammatory conditions
Pizarek et al.[165]	In vitro	Immunomodulatory peptide coating	IL-23 receptor antagonist coated to titanium surfaces to modulate cytokine expression in stimulated keratinocytes	IL-23Ra can modulate the immune response of oral keratinocytes by enhancing pro-regenerative cytokine expression and decreasing proinflammatory cytokine expression. These treated keratinocytes can also modulate THP-1 response leading them to M2 polarization

Two research groups investigated the potential immunomodulatory effects of antimicrobial peptides. Zhou et al. examined the immunomodulatory properties of GL13K,[161] a well-characterized antimicrobial peptide, when coated onto titanium surfaces. They found that GL13K coatings led to reduced proinflammatory cytokine levels in cells stimulated with lipopolysaccharides (LPS). In a related study, Zhuo et al. explored the effects of KR-12-3, another well-characterized antimicrobial peptide,[163] which also demonstrated immunomodulatory properties by lowering proinflammatory cytokine production in LPS-stimulated cells. The authors reported that the observed reduction in biofilm formation and antiinflammatory effects was associated with a decreased expression of specific genes. This trend of examining well-characterized antimicrobial peptides for additional immunomodulatory functions is promising, as these multifunctional molecules could potentially address multiple challenges in peri-implantitis prevention. Pizarek et al. have focused on a specific antagonistic peptide that blocks the IL-23 pathway. Findings indicated that this immunomodulatory coating not only reduced proinflammatory cytokine expression but also promoted keratinocyte-mediated macrophage polarization toward a pro-regenerative profile, thus potentially enhancing tissue regeneration. Other less specific peptides have also shown potential for macrophage polarization control and immunomodulatory potential.[162,164]

Immunomodulation around dental implants emerges as a strong strategy for incorporating technological and clinical advances to dental implant therapy and controlling peri-implant diseases. Nonetheless, even though these same therapeutic approaches have been extensively explored to treat periodontitis, much work still lies ahead to unravel biologically effective pathways that can be targeted to control inflammation around infected dental implants as well as to improve materials so that this biological knowledge can be exploited to its full potential and translated successfully to clinical scenarios.

6 | CONCLUSIONS

Significant advances have been made in the understanding and potential of novel locally delivered and immunomodulatory approaches for the prevention/treatment of peri-implant diseases. Nevertheless, their clinical application is still limited by a lack of control over the bioactivity afforded by the known delivery systems and the scarcity of consistent nonclinical and clinical data. Awareness must be raised on the part of the industry to develop feasible agents/tools to enhance the efficacy of preventive and therapeutic strategies.

AUTHOR CONTRIBUTIONS

All the authors conceived the concept and equally performed the writing.

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CONFLICT OF INTEREST STATEMENT

AM has received consulting fees from MagDent Technology (Israel).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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