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Microbiome and the inflammatory pathway in peri-implant health and disease with an updated review on treatment strategies

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ABSTRACT

Crestal bone preservation around the dental implant for aesthetic and functional success is widely researched and documented over a decade. Several etiological factors were put forth for crestal bone loss; of which biofilm plays a major role. Biofilm is formed by the colonization of wide spectra of bacteria inhabited around dental implants. Bacterial adherence affects the regulators of bone growth and an early intervention preserves the peri-implant bone. Primary modes of therapy stated in early literature were either prevention or treatment of infection caused by biofilm. This narrative review overviews the microbiome during different stages of peri-implant health, the mechanism of bone destruction, and the expression of the biomarkers at each stage. Microbial contamination and the associated biomarkers varied depending on the stage of peri-implant infection. The comprehensive review helps in formulating a research plan, both in diagnostics and treatment aspects in improving peri-implant health.

1. Introduction

Bone loss and structural damage occur when the extent of bone resorption within a basic multicellular unit exceeds the bone formation (negative bone balance).[1] Several exogenous (surgical or implant) and endogenous (host) factors were found to affect the success of the implant. Among the factors, traumatic surgery, bacterial infiltration, host's inherent healing capacity plays a major role in bone loss during the post-surgical healing phase.[1–3] Though bacterial adherence may not be the only etiology for crestal bone loss, exposure of a rough surface on the implant due to other factors like surgical or occlusal trauma have shown to favor bacterial adherence.[4,5]

2. Peri-implantitis

Peri-implantitis is often described as an inflammation of soft tissue along with bone loss of more than 0.5 mm.[6–8] However, there is a non-consensus statement on defining mucositis, wherein few authors suggest as only a soft tissue lesion whereas others suggest the presence of soft tissue lesion along with the bone loss of less than 0.5 mm similar to peri-implantitis.[9,10]

Peri-implantitis has been classified based on severity into early, moderate and advanced based on probing depth, bleeding on probing, and bone loss. Probing depth of 4 mm and bone loss of less than 25% constitutes early implantitis, probing depth of 6 mm with bone loss of 25–50% of implant length constitutes moderate peri-implantitis whereas probing depth of 8 mm with bone loss more than 50% of implant length constitutes advanced peri-implantitis.[11] Javier et al. classified the severity based on stages 1, 2, 3, and 4 with the bone loss of 3 mm, 3–5 mm, 5 mm, and more than 50% of implant exposure respectively.[12]

Abbreviations: CD14, Cluster of Differentiation 14; TNF, Tumor Necrosis Factor; TWEAK, TNF-related weak inducer of apoptosis; IL, Interleukins; RANKL, Receptor Activator of Nuclear factor Kappa-BLigand; RANK, Receptor Activator of Nuclear factor Kappa-B; OPG, Osteoprotegerin; CSF, Colony-Stimulating Factor; sRANKL, soluble Receptor Activator of Nuclear Factor-κB Ligand; MMP 8, Matrix MetalloProteinase 8; TIMP, Tissue inhibitor of Metalloproteinase; VEGF, Vascular Endothelial Growth Factor; PSMB 2, Proteasome subunit beta type-2.

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3. Prevalence of periimplantitis

Peri-implantitis among the dental implant patients were reported to vary between 1 and 47%.[13] The prevalence of mucositis that included only soft tissue inflammation was reported in the literature as 19%,[6] 65%,[8] and 39%.[14] Cecchinato et al. observed a prevalence of 65% when he included the soft tissue inflammation with bone defect of less than 0.5 mm[9] whereas Fransson et al. had a 90% prevalence when mucositis was considered as a bone defect of less than 0.6 mm.[10] However, Marrone et al. observed only 31% even though he considered the mucositis as soft tissue inflammation with bone loss less than 2 mm.[15]

Peri-implantitis reported in the literature that was not specified in the range of bone loss were 30.1%,[6] 24%,[7] and 9%.[8] In specific, 23% of prevalence was observed when bone loss of more than 0.5 mm, whereas 28% prevalence was observed in a study with more than 0.6 mm bone loss.[13] Marrone et al. observed 37% prevalence when bone loss of more than 2 mm was included,[15] while Zetterquist et al. had only 0.37% prevalence when peri-implantitis was defined as the bone loss of more than 5 mm.[16] A systematic review revealed a prevalence of mucositis and peri-implantitis to be 42.9% and 21.7% respectively.[13]

The anaerobic bacterial colonization and the bacterial products like lipopolysaccharides from the dental implant microgap cause the upregulation of cytokines that inhibit bone formation with an increase in osteoclast formation in otherwise healthy peri-implant cells leading to failure of the implant.[17,18] To prevent microbial colonization and to prolong the longevity of implant, knowledge on the peri-implant microbiota and the mechanism of biofilm formation is essential for planning treatment strategies. This proposed review enumerates the microbes in the peri-implant region, the mechanism of action, and the biomarkers in peri-implant bone loss with the treatment protocol available in literature.

3.1. Literature search

A literature search was conducted in Pubmed, Science Direct, Cochrane, IndMED, OVID, and EMBASE database in time range of January 2000 to December 2021. The review included the articles that discussed the microbial colonization, antibiotics in implant infection, preventive strategies that inhibit microbial formation around the dental implant. The search yielded 1464 articles relevant to the keywords and 109 articles were selected for this review based on the microbial agents and treatment strategies for dental implant. Among the 109 articles, 84 were clinical studies of which only 59 belonged to treatment strategies and 25 review article were included in the present literature review.

4. Microbiome around dental implant

The microbiome that affects the health of the peri-implant can be either primary or secondary colonizer. The predominant microbes based on peri-implant health status are enumerated in Table 1.

4.1. Microbiome around healthy implant site

Early bacterial colonization in a healthy implant site will be similar to the microbiome of the remaining natural dentition in the arch in approximately 6 months[17,18] and varies with the health status of the natural dentition.[19,20]The predominant bacteria in healthy implant sites were found to be *Pseudoramibacter alctolyticus*, *Veillonella*, *Actinomyces israeli*, *Cutibacterium acnes*, *Parvimonas micra* and *streptococcus* belonging to the genus of Actinomyces (7 species), Capnocytophaga (4 species), Neisseria (4 species), Rothia (3 species), and Streptococcus (5 species).[21,22]

The microorganisms *Neisseria mucosa*, *Fusobacterium nucleatum*, *Fusobacterium polymorphum*, and *Capnocytophaga sputigena* dominated the implant in the submucosal and subgingival microbiota at healthy sites.[20] Whereas, implant with the deepest probing depth was associated with higher levels of *Eikenella corrodens*, *Fusobacterium nucleatum*, *Borrelia vincentii*, *Porphyromonas gingivalis*, and *Parvimonas micra*.[20] Literature also suggests that the microbiota of peri-implant sulci was similar to tooth sulci when the sulcus depth was less than 4 mm from an implant-abutment junction.[23] However, the microbiota around unhealthy implants differed based on the level of infection(mucositis, peri-implantitis, and failing implant).[19,20]

4.2. Microbiome around peri-implant mucositis and peri-implantitis

Eikenella corrodens was found in higher levels around implants with mucositis compared with healthy sites, and the risk of implant infection was found to be independent of the presence of teeth.[20]*Porphyromonas gingivalis, Tannerella forsythia,* and *Prevotella intermedia* were part of peri-implant mucositis co-occurring network, indicating their potential biotic interaction with other microbes during the early stages of peri-implant diseases.[24]

A large aggregate of Gram-negative anaerobic bacteria, including *Fusobacterium nucleatum*, *Treponema denticola*, *Tannerella forsythia*, and the "black-pigmented bacteria" such as *Prevotella intermedia*, *Prevotella nigrescens*, and *Porphyromonas gingivalis* were found to be predominant in peri-implantitis similar to adult or refractory periodontitis.[20,21,25,26] These microbes belong to the red complex, often described as *peri-implant related complex (PiRC),* and were found along with *Filifactor alocis, Desulfobulbus* spp. *oral taxon 041,* and *T.lecithinolyticum.*[21] It was also revealed that *Eubacterium minutum* was abundant in co-occurrence analysis with *Prevotella intermedia* in the peri-implantitis group.[24] In addition to the above species, *Eubacterium nodatum*, *Eubacterium brachy*, *Eubacterium saphenum*, *Filifactor alocis*, *Slackia exigua*, *Parascardovia denticolens*, *Centipeda periodontii* and *Parvimonas micra* were isolated from peri-implantitis.[22,27] Also, the presence of a high level of asaccharolytic anaerobic gram-positive and gram-negative rods suggested

Table 1
Microbes around dental implant based on health status.

Implant Health Status	Predominant microbes	
	Gram positive anaerobes	Gram negative anaerobes
Healthy implant site	*Pseudoramibacter alactolyticus*, *Cutibacterium acnes*, *Parvimonas micra* and *Streptococcus*.[22]	*Veillonella*, *Actinomyces Israeli*[22] *Neisseria mucosa*, *Fusobacterium nucleatum*, *Fusobacterium polymorphum*, and *Capnocytophaga sputigena*.[20]
Mucositis	*Parvimonas micra.*[20]	*Eikenella corrodens*, *Fusobacterium nucleatum*, *Borrelia vincentii*, *Porphyromonas gingivalis*.[20]
Peri-implantitis	*Eubacterium nodatum, Eubacterium brachy, Eubacterium saphenum, Filifactor alocis, Slackia exigua, Parascardovia denticolens,* and *Parvimonas micra.*[22,27]	*Fusobacteria, spirochetes, Tannerella forsythia, Prevotella intermedia, Prevotella nigrescens, and Porphyromonas gingivalis.*[20,25] *Centipeda periodontii*[22,27] *Porphyromonas gingivalis, Treponema denticola* and *Tannerella forsythia.*[26]
Failing implant	*Peptostreptococcus micros.*[28]	*Porphyromonas gingivalis, Prevotella intermedia, Campylobacter rectus, Fusobacterium* sp., *Actinomycetemcomitans, Capnocytophaga* sp., *Treponema denticola.*[28]

Mucositis-soft tissue inflammation; Peri-implantitis- soft tissue inflammation along with bone loss; Failing implant-bone loss that does not respond to treatment.

that the conventional periodontopathic bacteria were not the only periodontal pathogens active in peri-implantitis.[22,27] Among all the species, *Fusobacterium nucleatum* was found to be the predominant species, not due to its increased presence, but because of its over-represented microbial pathway.[21]

4.3. Microbiome around the failing implant

The analysis of microbiota in failing or failed implants showed significantly elevated levels of *Porphyromonas gingivalis*, *Prevotella intermedia*, *Peptostreptococcus micros*, *Campylobacter rectus*, *Fusobacterium* sp., *Actinomycetemcomitans*, *Capnocytophaga* sp., *Candida albicans,* and spirochetes like *Treponema denticola*.[28] Early implant failures were associated with biological complications while late implant failures were associated with either biological or mechanical complications, hence their microbial population also gets varied. Early implant failure had minimal diversity in microbial species with more than 50% of the population belonged to the same species of *Fusobacterium, Aggregatibacter,* and *Gemella*.[29]Whereas, the late failures were associated with *Tannerella forsythia, Treponema* sp.,*Desulfobulbus* sp.,*Fretibacterium* sp. and *Pseudoramibacter alactolyticus*.[29] However, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* were found in both early and late failures.[29]

5. Mechanism of microbial adherence and inflammatory pathway

Biofilm formed by the colonization of microorganisms involves a series of steps, which includes Adhesion, Growth, Maturation, and Dispersion.[30][Fig. 1] The initial adhesion of bacteria to a surface occurs by electrostatic attraction followed by the secretion of extracellular polymers.[31] The rough surface of the host also promotes a mechanical adherence of the bacteria by mechanical retention.[5] The co-aggregation of bacteria requires specific signaling molecules that decide the species of bacteria that could adhere in the colony-forming unit. The aggregation of bacteria provokes an inflammatory response in the host tissue by forming a biomarker that either promote or destruct the biofilm formation. However, the production of extracellular polymers and maturation of the biofilm makes it resistant for antimicrobial therapy.[32] The combination of bacterial communication and host related inflammatory response promotes the biofilm formation and peri-implant infection. The basis of the biofilm formation at cell level needs to be understood to inhibit the preliminary process of bacterial adhesion and growth, which in turn prevents biofilm formation.

5.1. Quorum sensing in bacterial adherence and growth

Microorganisms develop a unique way of regulating their biofilm formation through Quorum sensing. Quorum sensing is an intercellular signaling molecule mediated prominently by the bacterial cell envelope that helps in its physiological process of surviving and its resistance development against antibiotics.[33] This also enabled co-operative division of work between different species of bacteria within the bacterial colony. The acclaimed interspecies interaction induces biofilm formation through Autoinducer-2, a universal quorum-sensing molecule that could be either a furanosyl borate diester or tetrahydroxy furan varing according to the species.[34] Autoinducer-2 of *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, the prominent pathogenic bacterium in peri-implant health,[35,36]showed a major role in intra and inter species interaction in enhancing the adhesion of the bacterium to the target surface.[37] Similar to the mechanism of Autoinducer-2, the Major Outersheath Protein of *Treponema denticola* was found to increase the co-aggregation with the *Porphyromonas gingivalis* and *Fusobacterium nucleatum*.[38] The long fimbriae(FimA) of *Porphyromonas gingivalis* promotes auto-aggregation[39,40] and co-aggregation with *Actinomyces viscosus* and *Treponema denticola*.[39,41] Metagenomic analysis and meta-transcriptomic analysis showed significant co-occurrence relation of *Solobacterium moorei* and *Prevotella denticola*, and were taxa specific to peri-implantitis with the higher activity of plasmin receptor/glyceraldehyde-3-phosphate dehydrogenase genes.[42]

The pathogen most recognized around the peri-implant region was found to have a cell-to-cell interaction that either promotes the growth or inhibits the microbes in the colony. These signaling molecules were also found to inhibit other bacteria that do not complement the colony. Bacterial communication of Lipo-oligosaccharide extracted from *Treponema denticola* had a greater inhibitory effect on NF-κB mitogen-activated protein kinase signaling pathways and induction of cytokine expression by *Tannerella forsythia* lipopolysaccharide.[43] In presence of CD14 and lipopolysaccharide-binding protein, lipo-oligosaccharide inhibited the *Tannerella forsythia* lipopolysaccharide by binding with human gingival fibroblasts.[43] Research also revealed that the presence of both *Porphyromonas gingivalis* and *Treponema denticola* inhibited transformation of *Streptococcus mutans NG8* and *LT11* and its bacteriocin production.[44]

5.2. Gene expression in soft and hard tissue changes

At the initial stages of bacterial infiltration, endotoxin produced by the bacterium has the potential to stimulate hemolytic and macrophagic activity on the host tissue, leading to peri-implant mucositis.[45]At the

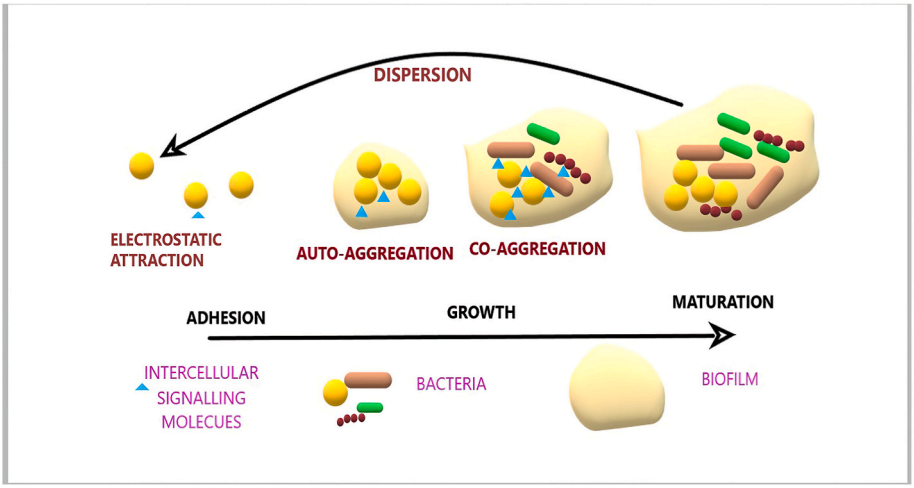

Fig. 1. Stages of Biofilm around implant.

initiation of an inflammatory response, macrophages, neutrophils, dendritic cells, and mast cells are released. Though host inflammatory responses are released to kill the microbial infiltration, their over-expression leads to negative bone balance [Fig. 2].Biomarkers of peri-implant disease had similarities with periodontal disease and the level of markers varied to a specific situation. A recent study states that TWEAK can be a potential biomarker in detecting gingivitis or peri-implant mucositis.[46] Host tissue exhibits its defensive mechanism by secretion of prominent proinflammatory cytokines like Interleukins(IL), TNF-α, and TWEAK.[46,47] Overproduction of the macrophages releases IL-1, TNF alpha that activates the osteolysis,[47] whereas transient action of neutrophils and mast cells has a positive effect on osseointegration,[45,48] but their abundance was also found in dental implant rejection. Despite the host defence mechanism, the virulence factor expressed by the bacterium helps in its growth on the target site and influences osteolytic activity in the peri-implant region. Glycosylated surface envelope of *Tannerlla forsythia*,[49] Cystalysin secreted by *Trepenoma denticola*,[50] and lipopolysaccharides from *Prevotella intermedia* and *Porphyromonas gingivalis*[25] cause a stimulatory effect on the macrophagic activity that matures the macrophages into osteoclast.

During the progression of the lesion from mucositis to peri-implantitis, the host releases higher levels of biomarkers such as IL, Sclerostin, RANKL, and OPG,[46,51] but it was also found that the OPG was significantly higher in the healthy peri-implant group.[52,53] Receptor activator of NF-kB (RANK), receptor activator of NF-kB ligand (RANKL), and osteoprotegerin (OPG) are the main components of this signaling system in progressing the peri-implantitis towards an osteolytic lesion. Sclerostin inhibits the signaling molecules that promote osteoblastic differentiation,[54]whereas Colony-stimulating factor (CSF)-1 encodes stimulation, the proliferation of macrophages, and maturation of osteoclast.[55] RANKL binds to RANK as its receptor and eventually leads to osteoclast precursor maturation,[56]but the secretion of OPG inhibits this binding and prevents osteoclastic formation.[56] Studies also reveal that the RANK is more in the peri-implantitis group, whereas sRANKL and OPG were more in the group affected with periodontitis.[52] On progression of inflammatory pathway, increase of enzymes like Cathepsin K, MMP-8 were observed during bone resorption.[57,58]

In addition to the above mentioned biomarkers, the C-telopeptide pyridinoline crosslinks of type I collagen (ICTP) were found significantly higher in the peri-implantitis group.[52]It was also observed that the Colony-stimulating factor (CSF)-1 was higher in the crevicular fluid of peri-implantitis individuals than those affected with mucositis, which aids in discriminating between early and late stages of peri-implantitis.[55]The biomarkers in peri-implantitis group triggered by micro-organisms had increased IL-1β and OPG levels in peri-implant crevicular fluid along with TIMP-2 and VEGF, but with no significant difference in enzyme MMP-8.[59]Recently, Molecular diagnostics identified miRNA hsa-miR-31–5p associated with PSMB2 to be the potential biomarker of chronic inflammatory stage.[60]The biomarker release indicates that the host prevents its self-destructive mechanism at the initiation of the lesion, but the virulence factor expressed by the microbiome progresses the lesion.

6. Antibiotic therapy and biofilm formation

6.1. Prophylactic antibiotic therapy

The focus of therapy to prolong the survival of the implant should be to prevent crestal bone loss before it could occur. Literature reveals the use of prophylactic antibiotics to prevent bacterial infection did not show any improvement in post-operative dental implant survival, especially in healthy individuals.[61,62] Abu-Ta'a M in 2008, observed that the antibiotics did not reduce microbial contamination and post-operative infections, but reduced post-operative discomfort to the patient.[63] The review of clinical studies exhibited a slight reduction in failure rate with the administration of single pre-operative antibiotics.[61–63] With the use of both pre and post-operative antibiotics, Abu Taa et al. showed a 4.2% decrease in failure rates, and on the contrary Gynther et al. showed a 1.1% increase in the failure rates.[61,63]

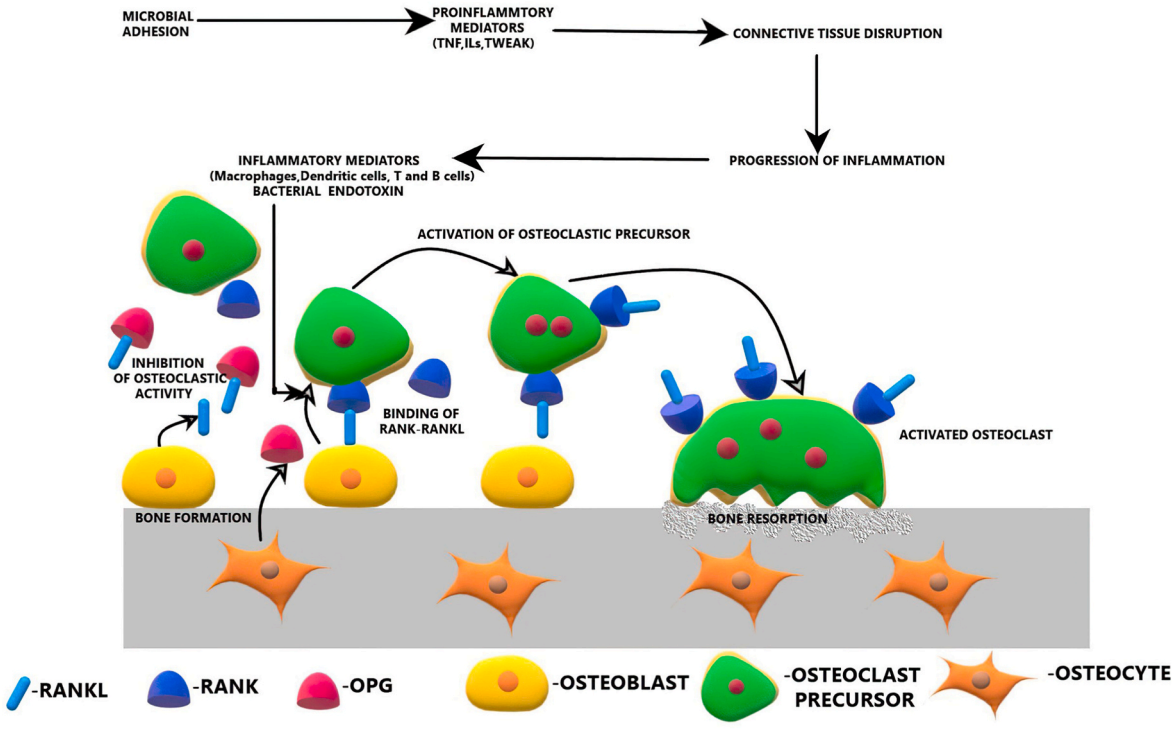

Fig. 2. Inflammatory pathway in peri-implantitis.

6.2. Local antibiotic drug delivery

For desirable outcomes, conventional antimicrobial therapy was delivered locally and complemented with other therapies to increase its efficiency. The treatment of severe peri-implantitis by non-surgical subgingival debridement did not show improvement with the combination of metronidazole and amoxicillin antibiotics.[64] Tetracyclines as a local drug delivery were found to be effective in the treatment of peri-implantitis.[65] Minocycline hydrochloride in drug delivery abutment and also as microsphere were found to be effective in preventing peri-implantitis.[66,67] The antibacterial impact of rifampicin-loaded microspheres coated over mesh implants, showed efficacy to significantly reduce postoperative implant infections due to the controlled drug delivery system.[68] Drug delivery systems such as nanocarriers, liposomes were tried for sustained release that improved the efficacy of antibiotics.[69–71] Alternatively the antibiotics were stimulated by supplementing with an electromagnetic field in orthopedic implant, low-frequency ultrasound, and photodynamic therapy.[72,73] The stated literature evidence were not evaluated for dental implants and hence need to be considered in future research.

6.3. Mechanism of action and development of resistance

The regulatory second messengers; cyclic di-GMP (cyclic dimeric guanosine monophosphate) and related cyclic (di)nucleotide play a key role in extracellular matrix regulation and bacterial adhesiveness to the surface.[74–76] The adhesive extracellular matrix released by the bacteria in the biofilm resists the antibiotic activity due to the presence of Cyclic di-GMP.[77] Though antibiotics release c-di-GMP phosphodiesterase to disintegrate the biofilm, at a sub-inhibitory concentration antibiotics like aminoglycoside inhibited c-di-GMP phosphodiesterase activity; inducing biofilm formation of *P. aeruginosa* and *Escherichia coli* (E. coli).[77] The sub-inhibitory concentration of antibiotics also promoted both gram-positive and gram-negative bacteria.[78,79]

Other reasons put forth in the development of antibiotic resistance were environmental heterogeneity, a mutagenic response by bacterial strain, the presence of non-dividing cells, and 'persister cells.[71,80–82] The presence of a small subpopulation of bacterial specific phenotype or 'Persister cell' in the bacterial colony develops temporary drug tolerance to antibiotics.[82] The antibiotics also have their restricted target on fast-growing bacteria and hence need the addition of synergistic compounds to prevent or remove the biofilm.[71]

Antibiotic therapy has the advantage to control and treat an infection, but the impreciseness in concentration and dosage may reverse its effect.[78,79] Moreover, the development of drug resistance, local and systemic complications are some of the disadvantages of using antibiotics. The focus on the prevention of bacterial infection with antibiotic prophylaxis gives contradictory results. Hence, it is essential to identify a new treatment strategy from infection control to the prevention of bacterial contamination with minimal/no adverse effects that would prevent bone loss.

7. Non-antibiotic antimicrobials and biofilm formation

The requirement of a rough surface implant to accelerate osseointegration favors nidus for bacterial colonization.[5] Dispersal agents, surface modifiers, zwitterions, metal ions, and electrotherapy are evolving towards biofilm prevention. However, the challenge for the usage of dispersal agents would be to identify a suitable delivery vehicle to prolong the duration of action which is yet to be researched.[83]

7.1. Coated implants

Altering the surface property of the implantable surface is an evolving discipline in bacterial repulsion. Coating the surface with silver, zwitterions, and polyethylene glycol was attempted.[84–86] The agents such as diamond-like carbon (DLC) exhibited an antimicrobial property. But, the implants coated with DLC neither showed changes in antimicrobial properties nor inhibited the infiltration of *E. coli* into the abutment-dental implant interface.[87,88] Bacterial loading at the level of the peri-implant tissue was controlled by coating the implant with an alcoholic solution containing polysiloxane oligomers and chlorhexidine gluconate at 1%.[89]

The natural antibacterial agent totarol was coated over the dental implant and abutment surfaces favored epithelial formation and prevented bacterial infiltration.[90] Visible-light-activated naturally derived polymer (gelatin) with an antimicrobial peptide (AMP) forms a hydrogel on curing over the implant surface. They were proved to exhibit significantly higher adhesion to physiological tissues and titanium surfaces promoting cell proliferation and had remarkable antimicrobial activity against Porphyromonas gingivalis.[91] An in-vitro evaluation of the sealing agent at the implant-abutment junction(Morse taper connection) prevented microbial infiltration of dual-species biofilms of *E. faecalis* and *C. albicans* at 14 days.[92]

7.2. Metal particles

Metals (gold, silver and iron, copper and magnesium), metal oxides (zinc oxide, iron oxide, titanium dioxide, and cerium oxide), and quantum dots (cadmium sulfide and cadmium selenide in nano form) were effective as antibacterial agents, but their bacterial spectra are limited and differed according to the type of the metal.[81,93–95] Silver, having an inherent antibacterial property was tried in various forms to improve the surface characteristics of an implant. Ti-GO-Ag nanocomposite (Titanium, Graphene oxide, Silver), a dual-functionalized implant biomaterial was antibacterial and biocompatible.[96] Zinc oxide nanoparticles were found to be effective in providing antimicrobial properties for both orthopedic and dental implant in-vitro.[97] Animal study revealed antimicrobial activity of a silver multilayer (SML) coating were good in orthopedic implant, however, a scarce deposit on lymph node and liver were observed without any deposit in blood or urine.[98]

7.3. Zwitterionic characterization

The concept of zwitterionic characterization involved the release of the dead bacteria that prevents fouling of the environment. Zwitterion at an isoelectric point has phase-changing potency to exhibit the kill-release mechanism. Poly(N,N-dimethyl-N-(ethoxycarbonylmethyl)-N-[2'-(methacryloyloxy)ethyl]-ammonium bromide) (pCBMA-1 C2, cationic precursor) with zwitterionic potential was grafted onto a gold surface, which prevented the proteins and the attachment of microorganisms to reduce the biofilm formation and repelled the dead bacteria.[85] Silver nanoparticles dispersed in the zwitterionic matrix were also identified as a potent antibacterial agent.[99]

7.4. Osteopromotive factor in anti-biofilm therapies

The biofilm inhibition discussed under preventive therapy did not focus on the effect of antimicrobials in bone growth/preservation and, cytotoxicity of the material to human cells and peri-implant bone. Bone morphogenetic protein widely used in intra-oral and extra-oral sites for inducing new bone formation, also has an indirect antibacterial property,[100] and can suppress infection in both animal and human model.[101,102] Varying the concentration of chitosan and BMP-2 and delivering with hydroxyapatite over titanium implant surface showed excellent osteopromotive and antibacterial properties.[103] Similarly, an

antimicrobial peptide derived from insulin-like growth factor binding protein-5 had both antimicrobial and wound healing capacity.[104] Though the mechanism behind this has not yet been thoroughly researched, our review suggests that the growth factors can prevent bacterial infection but, requires further research in this field.

Co-encapsulation of BMP with agents like silver nanoparticles, gentamycin, and vancomycin were identified to have osteopromotive and antibacterial properties.[105–107] Other growth factors which were tried in combination therapy with antibiotics were Platelet Rich Fibrin (PRF) and Insulin-like Growth Factor (IGF).[108,109] Addition of 5 mg/ml metronidazole; 150 mg/ml clindamycin; 1 mU/ml penicillin to PRF before centrifugation had reduced the postoperative infections.[108] Further review revealed that the optimized silver nanoparticle (AgNP)-coated collagen membrane (though not a growth factor) exhibited excellent anti-bacterial effects with potential induction of osteogenic differentiation of mesenchymal stem cells that guided bone regeneration.[110] Use of graphidyne (GDY) composite TiO_2 nanofiber through enhanced photocatalysis prolongs the antibacterial ability and also had superior osteoinductive abilities for cell adhesion and differentiation.[111]

8. Other agents in antimicrobial therapy for dental implants

Researchers had also evaluated the efficacy of electrochemical current and charged particles in preventing the formation of biofilm. The in-vitro use of electrochemically treated titanium implants showed a reduction of viable *Escherichia coli* counts in cathodic implants and complete disinfection in anodic implants at 7.5 mA and 10 mA.[112] A similar concept was tried with the positively-charged silver nanoparticles, and the Titanium Nitride surfaces showed the highest bactericidal activity against the limited bacterial species evaluated.[113,114] Negut I et al., in 2020, designed a functional bioapatite–biopolymer double nanostructure using matrix-assisted pulsed laser evaporation for long-term microbial eradication for more than 21 days.[115] Though long-term release has been observed, only two types of bacterial strains were evaluated for antibacterial activity. Moreover, the evaluation of the antibacterial activity of a biomaterial did not include our primary area of concern; enhancement of bone formation.

8.1. Limitations

This narrative review summarises the microbiome and the biomarkers observed in peri-implant health and disease based on information obtained through scoping search. Meta-analysis was not conducted due to the heterogenicity of the research article used in our review.

9. Conclusion

Crestal bone loss is a continuous process and bacterial colonization was found to occur in coherence with most of the other etiological factors. The inflammatory pathway around an implant is a complex mechanism and sound knowledge on the microbial pathway, and host inflammatory response is required in preventing the implant failure at an early stage. The presence of biomarkers such as inflammatory mediators, bone markers, and enzymes give comprehensive information on differentiating the early and late stages of peri-implantitis. Future research is required to be enhanced in the field of molecular diagnostics in identifying the stage of peri-implantitis. The biomaterial that was tried to prevent biofilm formation lacked the clarity in cytotoxicity of the host cells and its action on bone-forming cells. The review suggests that the growth factors like BMP could be used either alone or in congruence with other antimicrobial biomolecules.

Declaration of competing interest

The authors declare no conflict of interest.

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