Review Article

Antimicrobial surface treatment of titanium dental implants: a narrative review between 2011 and 2021

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Background and Objective: Development of methods to decrease bacterial contamination on oral penetrating devices has been increasing but has not born predictable results. The need for antimicrobial coatings for devices placed inside of the body, particularly penetrating devices that emerge inside the oral cavity is of profound interests to dentistry. Titanium dental implant surfaces, including the abutment-implant junction are associated with a relatively high incidence of chronic infection termed peri-implant disease. In fact, peri-implant disease is the most frequent complication of dental implant treatment. Therefore, a narrative review of the need for technological development to prevent or curtail peri-implant disease is presented.

Methods: A review of current English language literature published between 2011 and December 1st, 2021 was done in PubMed using the MeSH subject of anti-bacterial treatment of titanium dental implants. The Search librarian conducted the search at the American Dental Association Library in Chicago, Illinois. A further criterion was searched for sustained in vivo anti-microbial activity. There were no stringent selection criteria, such as removing fluoride treatment from the search, due to the limitation of articles in this nascent field.

Key Content and Findings: This narrative review summarizes the lack of publications that fulfill the search criteria with no surface treatment being shown to have a sustained antimicrobial effect. Therefore, there remains a need for extraordinary oral hygiene measures to delay gingival marginal instability, circumferential bone loss, papillary height instability and extension of peri-implant disease around the surface of the implant.

Conclusions: Antimicrobial surface treatments or coatings were reviewed, none of which have proven to satisfy present clinical needs including the use of antibiotic, silver or nitride coatings. No surface modification has shown a sustained anti-microbial effect to combat peri-implant disease.

Keywords: Peri-implant disease; periimplantitis; titanium surface; antimicrobial surface

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Introduction

The rational for this review is to determine progress on the critical need of curtailing or preventing peri-implant disease from oral biofilm on exposed titanium surface of dental implants. The incidence of peri-implant disease increases over time with long term studies showing an incidence exceeding 20% (1). A 9-year study in 588 patients showed a 45% incidence of bleeding on probing associated with bone loss including a 14.5% incidence of greater than 2 mm bone loss attributed to peri-implant disease (2). The net effect of

Table 1 The search strategy summary

Items	Specification
Date of search	12/1/2021
Databases and other sources searched	PubMed
Search terms used	Anti-bacterial treatment of titanium dental implants
Timeframe	2011–2021
Inclusion and exclusion criteria	Antimicrobial coating of titanium dental implants
Selection process	ADA librarian selected articles based on MeSH search criteria

ADA, American Dental Association.

periimplantitis is exposed titanium surface to the oral cavity from peri-implant bone loss which tends to progress long-term to implant failure (3-7).

Though there are many confounding risk factors, the dental profession is left with the problem of how to manage exposed titanium surfaces which accumulate difficult to remove microbial biofilm (8).

Hickok *et al.* described the potential impact of antimicrobial action at the implant surface delineating the use of three approaches including enhanced nano-topography, elution of antimicrobials to retard bacterial adhesion and bonding of pharmaceutical agents to the surface all of which at present have failed to affect a long-term antimicrobial function (9).

The key narrative review question is: Has there been an effective titanium surface treatment with long term antimicrobial activity to prevent peri-implant disease? And, if not: Is there a promising technology published that appears to be able to accomplish a significant reduction in peri-implant disease?

Whatever the exact mechanism of peri-implant de-osseointegration, which might include foreign body debris such as retained cement or sheared titanium particulate matter, once bone attachment is lost the device withstands continuous bacterial insult leading to osteoclastic bone resorption and progressive bone loss which likely does not reform even if the titanium surface is decontaminated and bone grafted (2-18).

Decontamination and regrafting of lost bone around titanium implants is possible but with highly variable result, not verified longitudinally and requires relatively invasive surgery (17,18). So, the loss of bone around implants even if treatable and manageable becomes a risk for implant failure (3-7).

There are five clinical findings associated with exposed implant surface which impact the dental health of a patient as follows:

(I) Continuous requirement for additional hygiene measures;
(II) Gingival margin instability;
(III) Circumferential bone loss progression;
(IV) Papillary height instability;
(V) Implant source extension of peri-implant disease.

The purpose of this article is to highlight the problem of exposed titanium in the mouth and the possible role of antimicrobial treatments on the existence and progression of peri-implant disease. We present the following article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-62/rc).

Methods

Though the manuscript is not a systematic review but a narrative review, we searched relevant literature with the following consideration (*Table 1*).

Results

There were 16 articles that met the initial criteria including 3 review articles for various antimicrobial coating treatments of titanium dental implants listed in *Figure 1*. Though these articles showed evidence of some antimicrobial efficacy either *in vivo* or *in vitro* there was no clear evidence for prevention of biofilm formation and therefore prevention of peri-implantitis. The number of articles, therefore, that showed a sustained antimicrobial activity for clinically significant efficacy was zero.

Key findings of literature review

The key findings were 16 articles including 3 review article that met the criteria of which none showed clinical efficacy to prevent peri-implant disease.

Limitations of research reviewed

The limitation of the research review was a search for clinically sustained efficacy of any significance which there was none. The vast majority of the articles that reported

Mukadden K *et al.* Nanostructure titanium. Materials 2021
Jennes ME *et al.* Systematic Review. Antibiotics 2021
Almohandes A *et al.* Ti-Bis-Gal Clin Oral Impl Res 2021
Lopez-Vlaverde N *et al.* Systematic review. Antibiotics 2021
Sterzenbach T *et al.* Bioadhesion Review Clin Oral Investi 2020
Odatsu T *et al.* Nano-Ag coating. Antiobotics (Basel) 2020
Zhang X *et al.* Ta-coated titanium. In J Nanomed 2019
Zho J *et al.* Sr-coated titanium. Sci Rep 2019
Brunello G *et al.* Zirc-nitride coating. PLoS One 2018
Ding L *et al.* Doxyclyline cdfoated titanium Dent Mat J 2018
Kheur S *et al.* Nano-silver coating. Colloids 2017
Huacho PMMM *et al.* Diamond-C coating. Braz Dent J 2017
Nie B *et al.* Bacitracin-titanium coating. Colloids 2017
Cardoso M *et al.* Diamond-C coating. J Periodontol 2016
Xing R *et al.* Doxycycline coating. Biomed Mater 2015
Elter C *et al.* PTFE-titanium. Int J Prosthodont 2011

Figure 1 Here shown is a listing of the 16 articles selected by the review of the literature over the past ten years, none of which demonstrated clinical efficacy to mitigate peri-implant disease.

antimicrobial effect were not *in vivo* suggesting a much too abbreviated search criteria if *in vitro* study was excluded.

Without antimicrobial-titanium function, what then?

The lack of antimicrobial function for a titanium implant surface leaves the clinician with the critical management challenge of reduced expectation for health, function and esthetics of the dental implant restoration as follows.

Five clinical findings associated with exposed implant surface which impact dental implant health

Continuous requirement for additional hygiene measures

Once an exposed implant surface occurs, particularly if gingival recession occurs, the rough surface becomes a strong plaque retainer and is difficult to keep clean. Inadequate oral hygiene coupled with sucrose intake leads to bacterial synthesis of insoluble exopolysaccharides (EPS) polymers which strengthen the biofilm making it resistant to antibiotics and leading to a dysbiosis anaerobic environment. In one study an EPS enriched environment favored growth of strict anaerobic species such as *Porphyromonas gingivalis* as biofilm transitioned from a commensal aerobic to a pathogenic anerobic milieu (19).

Smoothing off the surface of the exposed implant, removing screw threads and rough surface leaving a polished surface is somewhat less likely to accumulate plaque as the adhesion of bacteria is promoted by rough surfaces (18,20-22).

The process of macro-modification of exposed titanium, however, will likely add peri-implant titanium debris which could aggravate peri-implantitis similar to the use of ultrasonic scalers which have been shown to add titanium matter from titanium surfaces potentially leading to osteoclasis and foreign body reaction as is found with wear particles found in orthopedic metallosis. More important is to prevent pocket formation or reduce gingival pockets to 3 mm in order to minimize inflammation and pocket depth progression by promoting an aerobic environment (23-25).

A facial bone graft done at the time of implant placement might be lost from peri-implant inflammation leaving a dehiscence defect that can been debrided and regrafted with a hard or soft tissue graft in an effort to reduce inflammation (16,17). Bone grafting done successfully can arrest peri-implant disease extension but is not yet highly predictable (15).

Once exposed titanium occurs adjacent to another implant or close to a tooth risk for extension of the inflammatory lesion to adjacent attachment is possible requiring careful daily hygiene measures and other preventive care (26).

Gingival margin instability

Once marginal bone is lost and the titanium surface is not covered with bone gingival recession may occur. Recession is somewhat dependent on timing of implant placement, horizontal implant position and gingival biotype, with thin biotype individuals more susceptible to recession. Though there is not a one to one correlation between implant exposure and gingival recession there is a correlation, and sometimes recession is the initial finding when peri-implant disease is present (26-30).

Circumferential bone loss progression

Periodontal disease on teeth is site specific while peri-implantitis is implant specific. This is because there is a different pathway for progression of inflammation. That

is, on teeth, Sharpey's fibers insert perpendicularly into the cementum and once interrupted the pathway of the inflammation can go down the side of the tooth vertically via the ligament space but it can also go sideways and form a circumferential defect. With implants lesions are circumferential and not vertical for the most part as once the inflammatory infiltrate gets past the junctional epithelium the easiest pathway is horizontal, starting around the top of the implant, because the connective tissue fibers adhere to the implant with parallel fibers without insertion into titanium. Furthermore, peri-implant lesion accelerates in a non-linear fashion with greater inflammatory findings than found with typical periodontitis lesions including marked vascular proliferation, lesions extending to a position that is apical of the pocket epithelium and lesions not being surrounded by non-infiltrated connective tissue as is found in periodontitis (14,31,32).

Methods to eliminate pockets around implants must address this and can involve osseous recontouring, apically repositioned flaps or decontamination of the implant surface and bone grafting, the latter usually requires a barrier membrane and possible submersion of the implant for some time (33,34).

Papillary height instability

The gingival papilla has complex attachment between teeth that include vertical support from supra-crestal gingival fibers. There fibers are absent around implants and are especially deficient between two implants. However, another factor of importance is the osseous foundation of a papillae. When a muco-periosteal flap, including the papilla is reflected and re-sutured into place, if the bone support for a papilla is present the papillae will recover its initial anatomical presence. However, if the bone is absent significantly papillary height will not recover. So, the osseous foundation of the papilla is highly important when it comes to implants placed in close proximity to teeth or to each other. Current thinking is that an implant should be placed 2 mm away from a tooth and 3 mm away from each other. As crestal bone loss occurs around an implant, initially the proximate papilla may remain, but as more and more bone is undermined, papillary support is lost (35-38).

One of the most difficult things to treat is absence of adjacent maxillary lateral and central incisors. This is very difficult to treat with side-by-side implants because the papilla between two implants is difficult to mimic when compared to the opposite dentate setting. Therefore, practitioners have settled for placing one implant and cantilevering the lateral incisor to address this. Once two side by side implants have become involved with peri implant bone loss in this setting the papilla between them will be lost and will require much effort to recover, if possible at all (39-42).

Implant source extension of peri implant disease

Osseous infection that is chronic such as peri-implantitis may spread to adjacent healthy structures such as an adjacent implant or tooth. Therefore, implant source contamination from the abutment connection and implant surface when in proximity to another implant is an important consideration. For example, complete arch implant placement where multiple implants are placed in close proximity, although biomechanically sound, may add long term risk if implant connections are not accurate or implants are placed too close to one another (41,43).

How close should one implant be to another? Depending on the implant system three mm has been suggested. There is no scientific formula but if the zone of inflammation is about 1.5 mm and two adjacent implants are less than 3 mm apart the zones of inflammation may combine to create a larger lesion. This then, suggests a minimum (37,38,44-46).

The implant-abutment junction

The one-piece or tissue level implant has the least peri-implant inflammation when compared to standard bone level, two-piece implants. Moreover, abutment connections vary with efficacy at maintaining a sterile seal between the implant and abutment. *Figure 2* shows a very tight, 5 micron seal. *Figure 3* shows an example of an early development abutment connection gap approaching 20 microns that allowed for bacterial percolation during functional movement. Whereas the *Figure 2* implant-abutment junction shows the picture of an implant abutment interface gap which is smaller than the size of *E. faecalis* which is 1/2 micron in size. Hardware precision for bone level implants, therefore, is an important consideration for bacterial source for peri-implant disease (47,48).

When gap sizes exceed 2 to 3 microns, all oral bacterial species in the oral cavity are able to ingress/egress the implant abutment junction to populate the "zone of inflammation" potentially leading to dysbiosis.

In addition to a precision abutment connection, the use of platform switch to keep the zone of inflammation away,

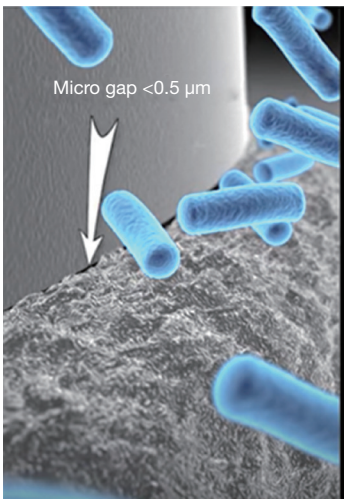

Figure 2 It is possible to precision manufacture abutment-implant interfaces to reduce or prevent access for bacterial contamination. Here shown is an abutment-implant interface with less than a 0.5 micron gap and illustrated potential bacterial contaminants (Courtesy and with permission of Ariel Zuhivitzky, Ditron Dental Ltd. Aschelon, Israel).

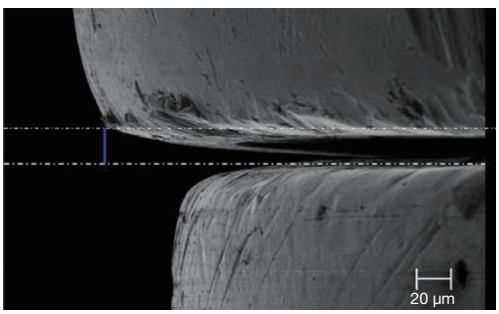

Figure 3 An abutment/implant interface is shown with a wide gap greater than 5 microns illustrating the potential for bacterial contamination at the junction leading to bacterial zone of inflammation and potentially dysbiosis (Courtesy and with permission of Dr. Marwan Mohamed Hendaway Cairo, Egypt).

the use of *platform bone switch* to increase bone mass at the cervical wall around an implant, a self-cleanable restoration and good oral hygiene measures—all impact the minimum distance required between implants. Great care should be taken in the decision to place side by side implants or placement of an implant into a tight interdental space such as a single lower incisor site that might encroach on the periodontal ligament space as the implant in itself and abutment interface in particular are a potential source risk for subgingival bacterial contamination (47-53).

Discussion and possible future solutions

The results of the key questions showed no clear evidence for any technique or process eliminating or curtailing long term contamination for titanium dental implants.

Given these risks of peri-implantitis in light of the findings discussed above, a change in the titanium surface capacity to become less likely to inflame or chronically infect local tissue could profoundly impact dentistry and ultimately change the way implants are placed including proximity to teeth and each other. In fact, there may be clinical situations in which implants are relatively contraindicated in which an implant that had antimicrobial capacity could then be implemented. There are four examples of this including: (I) patients with partial edentulism and recurrent periodontitis that is chronic but still not to the point of requiring removal of remaining teeth; (II) patients with osseous vascularity problems such as found in radiation treatment, bisphosphonate osteonecrosis history or high pack history tobaccos use; (III) multiple implant failure history and (IV) patients with failed bone grafting history particularly extensive vertical bone grafting that might be relatively unstable bone leading to remodeling exposure of implants over time—all these become relative indications for the use of an anti-microbial implant (54-57).

Periodontitis and dental implants

Perhaps the greatest indication for an antimicrobial implant is a history of periodontitis or ongoing periodontitis where implants are desired. The success rate of implants in partially edentulous patients who have had periodontitis can be nearly equal to patients without a periodontitis history if oral hygiene measures are strictly maintained. However, in patients with severe periodontitis, despite treatment and maintenance measures being optimal there is still a significantly increased incidence of peri implant disease over periodontally healthy patients.

So an antimicrobial implant will certainly open up opportunity for more frequent use in the compromised setting of previous or even present periodontal disease (58).

Compromised bone biology

Radiation treatment, bisphosphate history and tobacco use are patient histories that indicate possible compromise to

bone biology (59-61).

Radiation therapy causes vascular compromise to bone such that reflecting a soft tissue flap may expose non-vital bone that does not revascularize adequately leading to dehiscence and osseous necrosis. These settings are obviously not indicated for osteointegration unless subthreshold radiation doses or possibly the use of hyperbaric oxygen therapy are done to improve bone vitality. An early event leading to peri-implant bone loss in the radiation case may actually be from fatigue failure of nonvital bone with subsequent bone loss leading to exposure of titanium and secondarily, periimplantitis, which could be curtailed by the use of an antimicrobial implant (59).

Parenteral or prolonged oral bisphosphonate treatment either prior to or subsequent to implant placement can lead to loss of osteointegration due to osseous necrosis, a cofactor being secondary infection from exposed titanium implants. Placement of implants in patients on drug holiday or with a significant history osteoporosis treatment may warrant the use of antimicrobial implants (60).

The use of tobacco is important as it interferes with osseous vascularity as well as soft tissue attachment. The incidence of bone loss in patients who use tobacco is greater as is the incidence of periimplantitis and implant failure. Therefore, the option of using an antimicrobial implant may have a distinct advantage in tobacco users (61).

Adjacent disease

The need for an antimicrobial implant is not strictly for iatrogenic or compromised biology reasons. Inadvertent bone loss can occur physiologically or due to adjacent tooth infection transmitted to an adjacent implant which might include periodontitis, gingival abscess, or endodontic abscess.

Well controlled studies are interesting and important but often do not take into account the human factor leading to poorly placed implants or even iatrogenic placement including placement in non-ideal settings where implants might not thrive as well. In a way, these controlled studies remove risk and poor methodology as a matter of course leading to idealized and perhaps uncommon results. Therefore, the use of an anti-microbial implant could function as a failsafe mechanism in prevention or extension of peri-implant disease process in any practitioner's practice. The absolute indication for an anti-microbial implant then is for any oral penetrating dental implant which has a potential for inflammatory, traumatic or physiologic bone loss (62).

Coatings

The use of an antibacterial coating for a two-piece dental implant might optimally be at the abutment-implant connection, the hardware interface, instead of at the bone-implant interface along the sides of the implant where osseointegration occurs. Hypothetically, if this connection could be coated to prevent formation of biofilm this might go a long way towards prevention of peri-implant disease. Still, once implant surface of an implant becomes exposed for whatever reason coating technology would be needed there as well.

Antimicrobial coating of dental implants could occur in multiple ways including the use of antimicrobial peptides (AMPs), slow-release antibiotics, addition of heavy metals such as silver, and modification of titanium surface incorporating the use of antimicrobial organic compounds. However, almost any type of coating could potentially interfere with osseointegration (54,57).

Coating for implants is classified into passive or active depending on their mode of action. Passive coatings do not release product into the surrounding tissues whereas active coatings release agents into the peri implant environment. Examples of active coatings are antibiotics, metal ions and functional peptides that downregulate infection (63-67).

Passive coatings

Antimicrobial surfaces can be obtained by modifying the crystalline structure of the oxide layer. For example, bacterial adhesion is inhibited by ultraviolet light irradiation which hydrophilizes the titanium oxide surface. This process does not interfere with osseointegration (67,68).

Other passive coatings such as polymer coatings like polyethylene glycol inhibit bacteria when applied to titanium surface but osteoblast function is impaired requiring the use of additional bioactive molecules to restore cell function. Albumin has also been shown to inhibit bacterial adhesion on titanium surface (68).

Active coatings

The idea of coating implants with an antibiotic comes in part from the successful use of perioperative antibiotics. This includes the use of prophylaxis, intra-operative and post-operative prescription all of which have shown positive

effect on the healing and survival of osseointegrated implants. Antibiotics have therefore been covalently linked to implant surfaces however, optimal release kinetics remains unresolved. And, once the titer of the antibiotic depot falls below a certain threshold concentration efficacy is lost. So antibiotic release remains a timing delivery quandary (69,70).

Jennes' and Lopez-Valverde's systemic reviews of various antimicrobial coating methods found only 9 and 6 articles (4 in the last ten years) respectively that met their criteria for inclusion, most of which were invitro studies, none showing efficacy for peri-implant disease (71-88).

Antimicrobial organics

AMPs are naturally occurring substances that target and kill a broad spectrum of gram-positive and gram-negative bacteria, fungi, and viruses by disrupting cell membranes and causing cell lysis. AMPs are not prone to the development of pathogen resistance like antibiotics. AMPs can be active when free in solution or adsorbed onto a surface such as titanium and have been shown to have antimicrobial efficacy against *S. aureus* and *P. aeruginosa*. Streptococcal collagen-mimetic protein coating has also been shown to reduce bacterial adherence of *S. aureus* and *S. epidermidis*. Although AMPs show a low tendency to induce resistances, more and more AMPs are losing their antimicrobial effectiveness against various bacterial strains over time reducing the incentive to commercially fabricate bioactive coatings using AMPs (89-93).

Bactericidal nanoparticles

Nanoparticles ranging from 1–100 nm incorporating copper, zinc, magnesium and especially silver and gold display antimicrobial activity and are therefore possible candidate molecules for antimicrobial implant surface modifications. Nanomaterials are used to create unique surfaces with altered physical and chemical characteristics but one major toxicological concern is that nanoparticles are easily phagocytized and may affect intracellular function. In procaryotes nanoparticles disrupt cell membranes but can also cause inhibition of DNA replication by binding to DNA. Interestingly, antimicrobial specificity varies with the various metal ions leading to differing bacteria biofilm constituents that are altered. Free particles of titanium at nanoscale also effect cellular response biology (54,57,64,75).

Summary

A narrative review of the literature for the last ten years showed minimal or absence of antimicrobial action with time as most all studies were *in vitro* and not in vivo. There were no sustained treatments that were shown to prevent peri-implant inflammation and in fact, transient effects such as the use of antibiotic coatings, though pharmacodynamic had end-point inefficacy.

The need for antimicrobial capacity for oral titanium implants is well know because of the likelihood that over time titanium implant surfaces become exposed in the oral cavity. The time scale of these events can take years, something not addressed in any of these studies.

Once titanium becomes exposed in the mouth increased efforts are required for hygiene maintenance to mitigate increased risk for peri-implantitis and late term implant failure.

Though any titanium device in the body is at risk for bacterial contamination from hematogenous etiology with oral penetrating devices there is particular risk for local contamination.

Antimicrobial strategy, therefore, remains an important area of investigation and is an ongoing need to curtail the nearly endemic prevalence of peri-implant disease in this important discipline of dentistry.

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