REVIEW
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Scope of Silver Nanoparticles in Periodontal and Peri-Implant Wound Healing: A Systematic Review of Translation Research

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Abstract

Background: Nano-biomaterials have transformed traditional medicine and are now considered an essential part of modern medicine. The present systemic review aimed to highlight the scope of silver nanoparticles in periodontal and peri-implant wound healing with special emphasis on its antibacterial effects in the management of periodontal and peri-implant infection in in vitro and in vivo animal studies.

Methods: A computer search of electronic databases, mainly PubMed, was conducted with a combination of keywords. The investigation was limited to studies discussing the effects of silver or silver nanoparticles in periodontal regeneration and periodontal/peri-implant healing and/or disease.

Results: The search resulted in 1566 articles of potential interest. Twenty-one articles were included in the systematic review for analysis. Although with considerable methodological limitations, the in vitro and in vivo animal studies noted high antibacterial properties of silver nanoparticles without any toxic effects on the cellular structure. In vitro and in vivo small-animal studies have demonstrated the safety and antimicrobial efficacy of AgNPs in periodontal and peri-implant wound healing. However, the therapeutic potential of AgNPs in clinical situations has not been explored.

Conclusion: There is a need to establish animal models that are closer in soft and hard tissue response to humans to verify the safety and efficacy of silver nanoparticles. Owing to the potential risk of antimicrobial resistance with the contemporary antibiotics, unconventional therapeutic regiments, like silver nanoparticles, that are safe and have high antimicrobial efficacy should be tried as an adjunct in the management of periodontal and peri-implant therapy.

Keywords: Silver nanoparticles, antibacterial activity, periodontal wound healing, peri-implant disease

INTRODUCTION

With the integration of technology into medicine, understanding the disease mechanism and its cure has been significantly improved.[1] This merger has broadened the horizons of biomedical science, and now the concept of restoration and preservation of health is a reality.[2] Numerous nanotechnology applications in healthcare include diagnostic and therapeutic radiology, cell biology and delivery, tissue engineering, nanorobots, stem cell and organ therapy, genomics, intracellular devices, and biomaterials science.[3-5]

Since the introduction of nanotechnology in medicine and dentistry, significant progress has been noted in the clinical applications of biomaterials.[2] Nano-biomaterials have transformed the shape of traditional medicine and are now considered as an essential part of modern medicine.[2-6] Broadly, nanomedicine can be defined as *the application of nanotechnology in medicine*. Innovation is a continual process; every day, we appreciate new nano-biomaterials' applications with the idea that it is a new therapeutic toolbox for several health issues. Since its introduction to the biomedical market, numerous innovative

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applications of nanotechnology have been offered to improve the quality of life of humans worldwide.[7] Nanotechnology has enhanced our diagnostic and therapeutic abilities through its physical (nanoscopic size) and pharmacokinetic properties. It is primarily used as a drug delivery/release system and targets specific cells and tissues in gene therapy.[5,7,8] From simple diagnostic imaging to gene therapy in cancer patients, this technology has tremendously influenced and amended our understanding of the disease mechanism and its cure.[7]

Nanomaterials have gained significant importance in medicine and dentistry for the last few decades due to their innovative applications.[9] Active research in dentistry is underway to use nanotechnology in restorative materials as nanocomposite filling materials and also to prevent caries through remineralization or early enamel lesions.[10] Now, nano-biomaterials are widely used in cellular (bone and soft tissue substitutes) and tissue engineering (scaffoldings), coating of ceramics, and surface modifications of orthopedic and dental implants.[9,11,12]

Metals, especially silver in the form of silver nitrate, have historically been used as an antibiotic agent in ancient medicine for many centuries.[13,14] It was used in the form of hard solid for the treatment of chronic wounds and ulcers. Other applications include treatment of lachrymal and salivary fistula (also, skin and anal fistulae).[15] In the early 19th century, it was used in the form of a solution (mixed with linseed oil) and concentrated ointments, as a caustic agent to treat hypertrophied granulation tissues.[13,16] With the discovery of the microscope in the late 19th century, antibacterial properties of silver were extensively studied. An extensive review of the history of silver has been presented by Klasen (2000).[16]

Applications of silver in dentistry date back to the early 19th century, where it started its journey as a filling material with amalgam.[17] However, in recent years, with the advancement in nanotechnology, silver has become an emerging biomaterial and has broadened its scope of applications.[4,9] From nanocomposites (as nanofillers) to dental implant coatings, it has provided promising results.[18,19] Antimicrobial and anti-inflammatory applications of nano-biomaterials have been extensively investigated.[20] In this regard, silver and silver nanoparticles (AgNPs) in the prevention and or reduction of gram-positive and/or gram-negative bacteria have been successfully applied.[21] The aim of the present systemic review was to highlight the scope of sliver nanoparticles in periodontal and peri-implant wound healing with special emphasis on its antibacterial effects in the management of periodontal and peri-implant infection in in vitro and in vivo animal studies.

MATERIAL AND METHODS

To identify studies appropriate for inclusion in this systemic review, a computer search of electronic databases mainly PubMed was conducted with the following keywords: "SILVER AND GINGIVAL DISEASE," "SILVER NANOPARTICLES AND GINGIVAL DISEASE," "SILVER AND PERIODONTITIS," "SILVER NANOPARTICLES AND PERIODONTITIS," "SILVER AND PERIODONTAL," "SILVER NANOPARTICLES AND PERIODONTAL," "SILVER AND PERIIMPLANT DISEASE," "SILVER NANOPARTICLES AND PERIIMPLANT DISEASE," "SILVER AND ORAL BACTERIA," "SILVER NANOPARTICLES AND ORAL BACTERIA," "SILVER AND REGENERATION," and "SILVER NANOPARTICLES AND REGENERATION" without any language and time restriction. The present review was registered with the National Institute for Health Research—International Prospective Register of Systematic Reviews, registration number CRD42017081883.

The search was limited to studies discussing the effects of silver or AgNPs in periodontal regeneration and periodontal/peri-implant healing and/or disease. Manual searches of the bibliographies of all the retrieved articles were also performed to include additional eligible publications. The literature was screened independently in an un-blinded standardized way by 2 authors (A.S. and S.Z.) for relevancy of the topic and quality of the content. The eligible studies were identified using the inclusion and exclusion criteria specified for the research. The differences were resolved by discussion between the 2 authors; if no settlement could be reached, the third researcher (Dr. J.Z.—relevant to the research field) decided after a comprehensive review. The search strategy is given in the flow diagram (Figure 1).

Inclusion Criteria

- In vitro and in vivo human and/or animal studies that investigated silver or AgNPs to treat periodontal/gum/peri-implant disease.
- Studies investigated the efficacy of silver or AgNPs on oral/periodonto-pathic/plaque bacteria.
- Studies investigated silver or AgNPs in dental implants (surface coatings) and peri-implant disease.

Exclusion Criteria

- Studies investigated silver or AgNPs in other general dentistry procedures/products (restorative and prosthetic materials, adhesive).
- Studies investigated silver or AgNPs to treat other medical issues and infections (burns, skin, and eye infections).
- Review papers/case reports.

RESULTS

Literature Search

Using a combination of proposed keywords, the search resulted in 1566 articles of potential interest. After removing duplicates and studies not fulfilling the inclusion criteria, 48 papers relevant to the topic were assessed for full text. A PRISMA flowchart describing the number of studies included and excluded at the first and second levels, as well as the reason for their exclusion at the second level of selection,

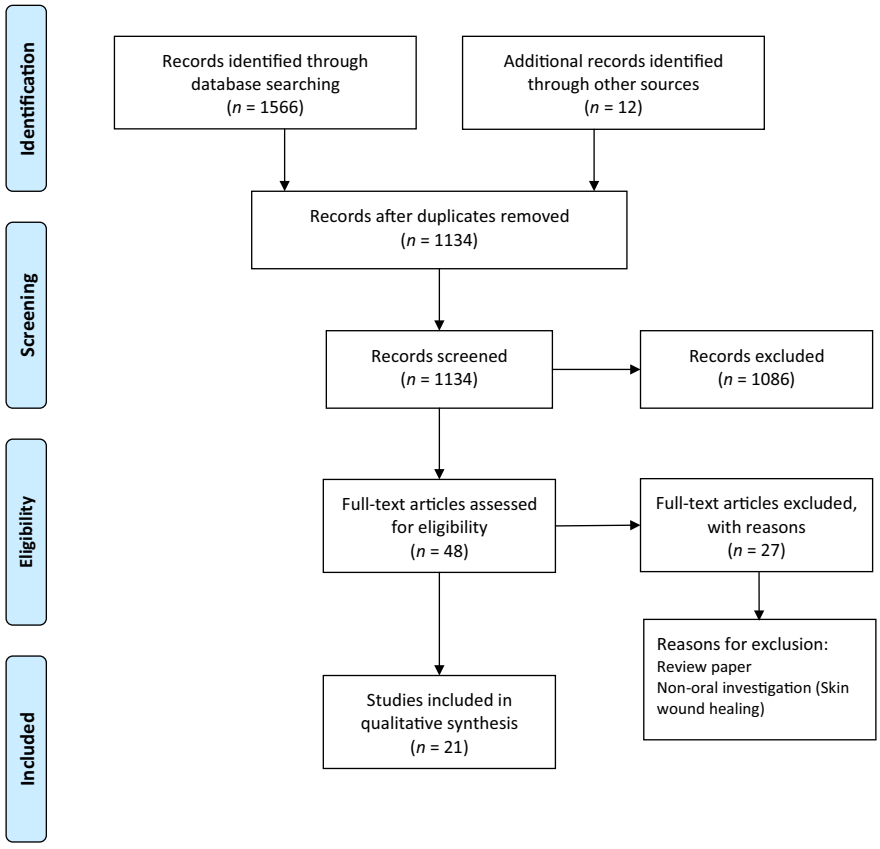

Figure 1. PRISMA 2009 flow diagram.

is shown in Figure 1.[22] Finally, based on the inclusion and exclusion criteria, 21 studies were included in the systematic review for analysis (Figure 1). Reasons for exclusion included the article was a review paper, case report, and non-oral investigation (skin wound healing).

Inter-Agreement Reliability

The inter-agreement reliability between the 2 reviewers was 97% (1531 out of 1578), 98% (1112 out of 1134), 95.8% (46 out of 48), and 100% (21 out of 21 studies) at the identification, screening, eligibility, and inclusion stages, respectively. Any discrepancies were resolved through discussion until a consensus was reached involving a third researcher (Dr. J.Z.). An array of methodological tools and formulations (types and size of particles) of AgNPs were employed; hence, the quality of included studies could not be assessed. Therefore, a narrative synthesis was carried out to describe the results.

Data search acknowledged that the majority of the work was conducted to explore wound healing (as dressings for burn wounds) and antimicrobial affectivity on skin wounds and plaque biofilms in the form of bandages, ointments/creams, mouthrinse, wafers, and nanoparticles. Besides, silver was extensively studied as an anti-cariogenic and restorative dental biomaterial. Search also noted studies that evaluated antimicrobial activity on titanium implants and/or titanium disks to prevent or manage peri-implantitis. The included in vivo animal studies were on beagle dogs, rabbits, and rats that investigated the antibacterial and healing capacity of AgNPs using polymerase chain reaction (PCR), micro computed tomography (μCT), energy-dispersive x-ray spectroscopy (EDS), radiographic and histological methods. The in vivo human studies analyzed reduction in periodontopathic bacteria. A detailed description of the studies included in the review is presented in Table 1.

Silver-Nanoparticles in Periodontal Wound Healing and Regeneration

The search identified 13 studies that investigated the effects of AgNPs at the cellular level including human dermal fibroblasts, human epidermal keratinocytes, periodontal ligamental fibroblasts, and inflammatory and growth mediators like interleukins, interleukin-12, tumor necrosis factor-alpha, matrix metalloproteinases, and vascular endothelial growth factor using cell culture and osteogenic differentiation cell-viability analysis looked into the effects of AgNPs on the periodontal ligament fibroblasts.[23] They concluded that AgNPs expedited osteogenic differentiation and inhibited infection.[23]

Table 1. Literature Included in the Review That Investigated the Effects of Silver Nanoparticles on Periodontal and Peri-Implant Healing

Researcher	Study Type/Aim	Study Method	Results	Conclusions
Bromberg et al.[27], 2000 Application: AgNPs in periodontitis management	In vitro and in vivo analysis (sustained release) of an antimicrobial agent over a 3 to 4-week period for the treatment of periodontitis.	SEM and EDS analysis—qualitative changes in wafer morphology In vivo clinical application of AgNPs in 9 patients with PD ≥5 mm each patient received 4 periodontal wafers (1 wafer/pocket). GCF analysis—total silver concentration (ppm) was investigated for each patient	EDS after 4 weeks—no silver was found in the wafers. In vivo application—most wafers disappeared past 3 days. Silver in the GCF of 28.8 mg/mL until at least day 21. Statistically significant reduction in the concentration of anaerobic bacteria ($P = .0078$), and a significant decrease in aerobic bacteria (*P*50.0547) from baseline (pre-treatment)—day 7.	The AgNPs wafers showed superior efficacy in the treatment of periodontitis. Adverse effects included minimal staining of hard and soft tissue staining 4/9 patients. Staining disappeared/polished away.
Cotton et al.[47], 2019 Applications: antibacterial efficacy of alpha-lipoic acid-capped AgNPs on HGF	In vitro sheep—cytotoxic effect of alpha-lipoic acid capped-AgNPs (6 nm) on HGH and compared with ionic silver and clinical antiseptics (CHX).	The MIC and MBC were established for a range of oral-related bacteria (*Escherichia coli*, *Streptococcus mutans*, *Streptococcus Mitis*, and *Staphylococcus aureus*)	Cell viability decreased with increasing AgNP concentration, whereas lower concentrations of AgNPs, (≤5 μg/mL) caused a significant increase in cell proliferation at 24- and 72-hour time points.	Alpha lipoic acid-capped AgNPs possess limited cytotoxic activity to HGF cells as compared to clinically utilized oral antiseptics (CHX) at the same time maintaining a broad range of antimicrobial effects.
Diniz et al.[48], 2016 Application: Antimicrobial activity against *Aa*	In vitro analysis—Antimicrobial activity against a common periodontal pathogen (*Aa*) and to promote bone formation.	Stem cell viability, proliferation, and osteo-differentiation capacity were analyzed. Silver activity against *Aa* was investigated. SEM analysis to investigate the morphology of the alginate scaffolds and encapsulated cells.	After 24 and 72 hours, all Silver Lactate (SL)-loaded alginate concentrations were able to significantly ($P < .05$) reduce the *Aa* bacterial load. After 5 days, the antimicrobial activity against *Aa* suspensions was no longer observed for SL-loaded alginate with concentrations less than 0.5 mg/mL.	Encapsulated GMSCs in SL-containing alginate hydrogel successfully differentiated into osteogenic tissue. It can be used as a novel treatment modality for biofilm-mediated peri-implant bone loss.
Dong et al.[31], 2017 Application: Peri-implant infection TNT	In vitro assessment Low pH-triggered silver-releasing Titania nanotube arrays - acetal linker (TNT-AL)-AgNPs implant to control peri-implant infection. Effect on osteoblast morphology and differentiation in vitro.	SEM, Transmission Electron Microscope(TEM), Atomic Force Microscopy (AFM), Fourier Transform Infrared Spectroscopy (FTIR), Cell proliferation and differentiation assay AgNPs-releasing TNT implant for peri-implant infection control—tested antibacterial efficiency of the released AgNPs.	TNT-AL-AgNPs implant exhibited enhanced osteoblast proliferation, differentiation, and did not affect osteoblast morphology in vitro	The novel design of the implant was found biocompatible and osteoinductive.
Emmanuel et al.[49], 2015 Application: Antibacterial activity	The antimicrobial activities of green synthesized AgNPs and drug-blended AgNPs were investigated against *S. mutans*, *Staphylococcus aureus*, *Lactobacillus acidophilus*, *Micrococcus luteus, Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *and Candida albicans*.	Well-diffusion assays were used. Wells with antibiotics Azithromycin and Clarithromycin and AgNPs alone maintained as a control	AgNPs showed antimicrobial activity against fungal as well as bacterial cultures. The antifungal efficacy of nanoparticles is very significant against *Candida albicans.*	AgNPs and drug-blended AgNPs showed a significant antibacterial and antifungal activity.

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Table 1. Literature Included in the Review That Investigated the Effects of Silver Nanoparticles on Periodontal and Peri-Implant Healing (*Continued*)

Researcher	Study Type/Aim	Study Method	Results	Conclusions
Flores et al.[50], 2013 Application: Antibacterial activity and cellular effects	Action of citrate-capped AgNPs on Gram-positive and Gram-negative bacteria in 2 different situations: (i) dispersed AgNPs (to assess their effect against planktonic bacteria) and (ii) adsorbed AgNPs on Ti substrates (to test them against sessile bacteria).	Cytotoxic effects of AgNPs on an osteoblast cell line (UMR-106) and several surviving cells were quantified.	Planktonic *Pseudomonas aeruginosa* showed a higher susceptibility to Ag than *S. aureus*, while for sessile bacteria, similar results are obtained for both strains. *P. aeruginosa* was found susceptible to 6 nm citrate-capped nanoparticles than *S. aureus*.	AgNPs showed antimicrobial effects on both Gram-positive and Gram-negative bacteria without affecting the viability of the osteoblasts.
Franková et al.[51], 2016 Application: Cellular effects of AgNPs	In vitro examination of the impact of AgNPs on human dermal fibroblasts, human epidermal keratinocytes and interleukins, growth factors, and MMPs	ELISA or Western blot incubation with AgNPs (for 24 and 48 hours) was assessed.	AgNPs decreased the formation of inflammatory cytokines (TNF-α and IL-12) and growth factors (VEGF). The production of MMP (MMP-3) by NHEKs after 24 hours at all of the tested concentrations was also reduced.	AgNPs improve wound healing.
Geng et al.[52], 2017 Application: Ag coated implants	*In vivo* animal study (36-Wistar rats). Impact of the silver coating was assessed after 2, 6, and 12 weeks *in vivo*, To investigate the effects of silver on bone healing.	X-ray, μCT and histological measurements to investigate quantity and quality of bone after silver-coated and uncoated titanium scaffolds after a healing period of 2, 6, and 12 weeks	No difference in bone ingrowth was observed between the Ti and Ti-Ag groups. Significant differences were not found between the titanium and silver-coated groups	AgNPs-coated porous titanium implants showed comparable bone formation and osseointegration to that of the uncoated implants after 2–12 weeks. Bone-implant interface showed silver was present primarily in the osseous tissue and was co-localized with sulfur.
Godoy-Gallardo et al.[53], 2016 Application: Antibacterial-coated dental implants peri-implantitis	In vivo (beagle dogs) investigation to see the effect of antibacterial-modified dental implants in the first stages of peri-implantitis (ligature-induced peri-implantitis)	Thirty dental implants in 5 beagle dogs—Investigated using μCT, backscattered SEM, histomorphometric and histological analyses, and ion release measurements were conducted—3 groups • Ti (untreated implants, 10 units) • Ti-Ag (silver electrodeposition treatment, 10 units) • Ti-TSP (silanization treatment, 10 units)	X-ray, SEM, and histology images showed that vertical bone resorption in treated implants was lower than in the control group ($P < .05$). Silver was found in the tissues around dental implants that were treated with silver. Ti traces were also identified for all samples.	Antibacterial surface treatments with the silver technique used showed a positive effect against bone resorption in peri-implantitis. Histology suggested that this silane may increase osseointegration.
Habiboallah et al.[54], 2014 Application: Periodontal surgical wound healing	In vivo animal study—30 female rabbits Randomized allocation—no periodontal disease	Gingivectomy was performed—Histological changes were monitored in days 4 and 7 after surgery to evaluate the inflammatory and repair stage of the healing process.	A significant difference in the inflammatory and repair parameters was noted. AgNPs dressing in general terms showed complete healing one week after the procedure.	AgNPs dressing showed positive therapeutic effects—accelerated surgical wound healing.

Table 1. Literature Included in the Review That Investigated the Effects of Silver Nanoparticles on Periodontal and Peri-Implant Healing (*Continued*)

Researcher	Study Type/Aim	Study Method	Results	Conclusions
Howell et al.[28], 1990 Application: Antibacterial effect on plaque formation	In vivo (12 beagle dogs) reduction of plaque formation and gingivitis was studied over 14-week period.	Scaling and root planning and pumice application for the plaque-free state. After that, three groups - • 4 dogs with topical applications of 3% zinc sulfadiazine × 2 daily • 4 dogs with 2% silver sulfadiazine • 4 dogs as control For a 14-week treatment period	Zinc and silver sulfadiazine-treated dogs showed a significant decrease in the gingival index and bleeding sites at week 2. For plaque index, a considerable reduction was noted as compared to controls at week 6.	Zinc and silver sulfadiazine inhibit plaque formation and reduce gingivitis. Experimental groups also showed a reduction in the probing depths (after 10 weeks of treatment)
Liao et al.[30], 2010 Application: Titanium implant surfaces coated with Ag— gingival fibroblasts	Biological activities of the novel antibacterial titanium implant surface. Antibacterial anti-adhesive property of Ti-nAg surface and proliferation of human gingival fibroblasts (hGFs) on Ti nAg and Ti (control) surface.	The anti-adhesive activity of the Ti-Ag surface towards *Pg.* SEM Cyto-compatibility assays were used for qualitative analysis	No cytotoxicity to the human gingival fibroblasts was noted for Ti-nAg. *Pg* and *Aa* showed a marked reduction in the adhesion on the Ti-nAg surface, compared to the polished titanium surface. The nanosilver-modified Ti surface showed excellent antibacterial activity and minimal cytotoxicity on cultured HGFs.	Ti-nAg showed good antibacterial properties and uncompromised cytocompatibility and can be used as an implant material
López-Píriz et al.[29] 2012 Application: Implant abutment peri-implantitis	In vivo animal study (5 beagle dogs)—3 implants were installed in each quadrant of the mandibles. Bone loss at implant abutments coated with a soda-lime glass containing AgNPs (experimental peri-implantitis).	Cotton floss ligatures were placed in a submarginal position around the abutment necks. After 15 weeks the dogs were sacrificed. Radiographs of all implant sites were obtained at the beginning and the end of the experimentally induced peri-implantitis.	The radiographic examination indicated that significant amounts of additional bone loss occurred in implants without biocide coating, considering both absolute and relative values of bone loss.	Soda-lime glass/nAg coatings on abutments have the potential to prevent peri-implant diseases
Munger et al.[44], 2014 Applications: Clinical influence	Healthy subjects (n=60) 10-32 ppm AgNP solutions were investigated in a controlled, single-blind, cross-over manner.	Blood counts, urinalysis, sputum induction, and chest and abdomen MRI were done. Silver serum and urine content were investigated. MRI of the abdomen and heart was also obtained (at the end of each phase of each period).	No clinical changes in the metabolic, hematologic, or urinalysis measures were noted. Similarly, no morphological and structural changes were identified in the heart, lungs, or abdomen.	Human oral dosing of a commercial oral AgNP colloidal solution for 2 weeks does not produce any toxicity markers.
Pokrowiecki et al.[55], 2017 Application: Antibacterial effect on Titanium disks	In vitro investigation of Titanium disks incorporated with AgNPs over different periods by Tollens reaction.	The surface roughness, wettability, and silver release profile of titanium discs were analyzed.	The addition of AgNPs significantly increased the surface roughness and decreased the wettability in a dose-dependent manner. These surfaces were significantly toxic to all the tested bacteria following a 48-hour exposure, regardless of silver doping duration	The presence of AgNPs on the titanium provides antibacterial activity against bacteria associated with peri-implantitis.
Prasetyo et al.[26], 2019 Application: Periodontal dressing for wound healing	In vivo animal study (24 rats) and divided into 4 groups to determine the effect of periodontal dressings containing AgNPs	Investigated the inflammatory parameters using 99mTc-ciprofloxacin (radio-pharmaceutical combination). After 1 hour of the IV injection, the rat was sacrificed. Single Channel Analyser was used to determine the accumulation of 99mTc-ciprofloxacin.	AgNPs dressing group showed that on the fourth day, there was already an anti-inflammatory response from the body against AgNPs.	AgNPs in periodontal dressing helped wound healing.

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Table 1. Literature Included in the Review That Investigated the Effects of Silver Nanoparticles on Periodontal and Peri-Implant Healing (*Continued*)

Researcher	Study Type/Aim	Study Method	Results	Conclusions
Rani et al.[24], 2015 Application: Antibacterial action in GTR membrane	In vitro investigation to evaluate the effect of AgNPs impregnating GTR membranes (bacterial adherence to GTR membranes and specific bacterial penetration through GTR membranes)	Mechanical properties, stress-Strain behaviour of collagen membranes were analyzed. Three groups were • GTR-C: Plain membrane as a negative control • GTR-NS: Membrane impregnated with AgNPS as the test group • GTR-DOX: Membrane impregnated with 25% (w/w) doxycycline hydrochloride—positive control.	AgNPs showed comparable, outcomes over doxycycline. GTR—with AgNp showed lower adherence scores than GTR-DOX (all 4 microorganisms, although, non-significant).	Adding AgNP into GTR membrane may prevent infection.
Shao et al.[25], 2019 Application: Antibacterial efficacy / healing around 3 types of membrane	In vivo animal (rat) study to Investigate antibacterial efficacy. Investigated wound healing ability of AgNPs in membranes.	In vivo antibacterial test in 42-male rats (randomly assigned to 3 study groups (n=7) with 2 sacrifice time points, i.e. day 7 and day 28) were investigated. Histological analysis was conducted.	AgNPs did show any change in the wound healing rate and tissue response. Histologically no significant differences were noted in the wound area among all membrane groups for collagen formation, vessel density, and macrophage density.	AgNP incorporation can improve the antibacterial efficacy of biomaterials without changing the wound-healing ability of chitosan-based membranes (investigated material)
Svensson et al.[56], 2013 Applications: Implant coatings	In vivo animal study (rabbits) to compare bone response between noble metal coated implants and standard Ti implants (machined).	SEM and interferometry measurements and histological analysis were conducted. Screw-shaped implants, 4 mm in length and 3.75 mm were placed in 16 white rabbits—Each rabbit received a total of 4 implants: 2 in the femur and 2 in the tibia; coated implants in one leg and control implants in the other.	SEM analysis showed differences in the qualitative surface topography between the groups. No histological differences in the groups were noted. Bone-implant interface was similar for coated and controlled implants	The coating does not impede osseointegration. Increased resistance to infection was noted. No adverse events were noted.
Vargas-Reus et al.[57] , 2012 Applications: Peri-implant pathogens	Antimicrobial activity of nano-particulate metals and metal oxides against 4 Gram-negative species of bacteria associated with peri-implantitis investigated	The activities of AgNPs were assessed by minimum inhibitory (bacteriostatic) concentration and minimum bactericidal concentration determination against *Prevotella intermedia, Porphyromonas gingivalis, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans.*	A dose-dependent and rapid antibacterial response was noted. The bacterial reduction was significant and reached 100% at different time points.	The bacteriostatic activity (MIC determinations) shown by the composites is indeed more significant compared with that of the nanoparticles alone.
Xu et al.[23], 2019 Application: Cellular (HPDFs) effects of AgNPs	In vitro investigation to evaluate the effects of AgNPs on osteogenic differentiation of HPDLFs, and investigate the underlying mechanisms of AgNPs activity.	The effects of AgNPs on the osteogenic differentiation were analyzed using cell culture, osteogenic differentiation cell viability, real-time PCR, and detection of active RhoA, was investigated.	AgNPs facilitated osteogenic differentiation of HPDLFs through the RhoA–TAZ axis of HPDLFs. The effects of AgNPs on osteogenic differentiation were repealed by a RhoA pathway inhibitor, C3 reagent.	AgNPs facilitated osteogenic differentiation and prevented infection. AgNps can be used as a potential agent for periodontitis treatment as an adjunct.

Aa, *Aggregatibacter actinomycetemcomitans*; AgNPs, silver nanoparticles; ALP, alkaline phosphatase; CHX, chlorhexidine; EDS, energy-dispersive x-ray spectroscopy; GTR, guided tissue regeneration; HGF, human gingival fibroblasts; HPDLFs, human periodontal ligament fibroblasts; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; NHEKs, normal human epidermal keratinocytes; PCR, polymerase chain reaction; *RhoA*, Ras homolog gene family member A; SEM, scanning electron microscopy; TAZ, Tafazzin; Ti, titanium; TNT, titania nanotube arrays.

(*Continued*)

Rani et al[24] (2015) in an in vitro analysis noted that AgNP-impregnated guided tissue regeneration membrane may be an effective way to prevent membrane-related infection. Two recent studies using a rat model investigated periodontal wound healing using membrane/CoePak infused with AgNPs and reported improved therapeutic outcomes.[25,26]

In a clinical investigation involving 9 patients with ≥5 mm of periodontal pockets, Bromberg et al[27] noted that sustained release of silver ions resulted in a significant reduction in anaerobic bacteria with superior outcomes in treating periodontitis.[27] Similar findings were also pointed out in a beagle dog study. The application of silver sulfadiazine resulted in the inhibition of plaque formation and reduction in gingivitis and probing depths after 10 weeks of therapy.[28]

Silver Nanoparticles and Dental Implants/ Peri-Implantitis

Eight studies that investigated the effects of AgNPs on dental implant surfaces/titanium disks were included in the review for analysis. Silver nanoparticle–coated dental implant surfaces were tested for increased antibacterial and wound healing capacity in several in vitro and in vivo animal studies. A beagle dog study reported improved antibacterial and bone level preservation with AgNPs. Similar enhanced outcomes were reported in another beagle dog study that investigated bone loss around implant abutments coated with a soda-lime glass containing AgNPs.[29] Other in vitro studies that analyzed antibacterial properties of titanium-nanosilver implant surface against *Aggregatibacter actinomycetemcomitans* (*Aa*) and *Porphyromonas gingivalis* (*Pg*) noted excellent antibacterial properties with these modified surfaces.[30]

A recent in vitro study looked into the low pH-triggered silver-releasing titania-nanotube array implant and noted that these modified implant surfaces are osseoinductive and have the potential to control peri-implant infection.[31] In summary, these in vitro and in vivo animal studies, although with considerable methodological limitations, noted high antibacterial properties of AgNPs without any toxic effects on the cellular structure.

DISCUSSION

Several translational preclinical efforts have been made to explore the antimicrobial activity, effects on plaque biofilm, and wound-healing capacity of AgNPs in periodontal and peri-implant healing. The review identified that AgNPs had been successfully used to prevent or minimize the occurrence of periodontal and peri-implant infections. Also, surface modifications of titanium implants or disks with AgNPs have shown enhanced bone response and improved antibacterial activity against periodontal bacteria. The majority of the studies have analyzed AgNPs as an anti-cariogenic material in restorative materials, in the sterilization of root canals in endodontic procedures, in acrylic resins in the fabrication of prosthesis, and in the orthodontic adhesive materials as fillers and as an aid in the regenerative membranes.[3,32,33]

Although in vitro and in vivo animal studies have demonstrated successful therapeutic outcomes of AgNPs, the current review noted only one human clinical study that investigated the sustained-release silver wafers in the periodontal pockets.[27] The gingival crevicular fluid analysis of 9 patients showed that periodontal wafers released bioactive silver for 3 weeks resulting in a significant reduction in anaerobic microbes, especially *Pg*.[27] Howell et al.[28] on the other hand, used a beagle dog model and reported that an application of 2% silver sulfadiazine twice a day resulted in a significant reduction in gingival inflammation and plaque formation after 6 weeks.

Significant improvements have been made to enhance the stability of AgNPs using different capping agents to avoid oxidation of metallic silver, that is, to delay the process of dissolution and aggregation.[20,32] Although a precise mechanism of antibacterial activity of AgNPs is not well-understood, it has been suggested that it causes bacterial cell wall damage, interacts with the bacterial cytoplasm, prevents DNA replication, involves in the disruption of bacterial protein, releases free silver ions, and generates reactive oxygen species.[3,4,20] Furthermore, AgNPs act on a broad range of bacterial targets, hence the potential for the development of antimicrobial resistance is quite rare.

Several studies have highlighted the potent antimicrobial effects of AgNPs on *Staphylococcus aureus* and *Escherichia coli*. Besinis et al[33] investigated the antibacterial effects of silver, titanium dioxide, and silica dioxide nanoparticles against *Streptococcus mutants* and compared them with 0.5% (v/v) chlorhexidine digluconate. They found the effect of 100 mg/L AgNPs in the media was 30 times more potent compared with chlorhexidine against *S. aureus.* They concluded that AgNPs were the best antibacterial agents against *S. aureus* when compared with the conventional chlorhexidine.[33] Similar findings were reported by Lu et al[34] (2013) who investigated the antimicrobial activity of AgNPs (of 3 different sizes 5, 15, and 55 nm) against 5 anaerobic oral pathogenic bacteria; *S. mutants*, *Streptococcus sanguis*, *Streptococcus mitis*, *Aa*, *Fusobacterium nucleatum*, and aerobic bacteria *E. coli*. They noted a better antibacterial effect against aerobic bacteria compared with that of anaerobic bacteria.[34]

A potential barrier in the widespread use of AgNPs is their ability to cause harmful cellular effects that have been documented in vitro and in vivo animal studies. In this regard, several in vitro studies working on kidney, liver, neural, and fibroblast cell lines noted enhanced oxidative stress, thrombosis, hyper-inflammatory response, and genotoxicity resulting in cellular damage.[35-37] Release of free silver ions from AgNPs has been shown to affect sensory organs by causing mitochondrial dysfunction in a dose- and time-dependent

manner.[38] Additionally, smaller size particles may cross the blood–brain barrier and accumulate in the brain and may adversely affect mature neurons.[39] Also, at higher doses, AgNPs stay in other body organs like liver, kidneys, lungs, and testis and result in the structural alteration of these organs. There, these particles penetrate the cellular membranes and cause apoptosis and reduction in cell viability.[4] Several in vivo animal studies using rat models confirmed the retention of AgNPs in multiple organ systems like in the kidney, liver, and spleen. However, a high concentration was excreted in the feces (>99%) and urine (<0.1%) within 4 weeks.[40-42] Brandt et al.[43] in a murine model, investigated the percutaneous absorption of AgNPs and found lower concentrations of these particles in inner organs (lung, liver, kidneys, and spleen), blood, and feces.

In contrast, Munger et al.,[44] in an in vivo human study evaluated the clinical, metabolic, and hematologic changes after the oral administration of AgNP colloidal solution (10 ppm—36 participants and 32 ppm—4 participants) in 60 healthy participants.[44] The study did not find any observed clinical and/or hematologic toxic effects of the tested solution. Research also acknowledges that smaller doses of AgNPs are nontoxic to human cells.[45] An important limitation of the current review is scarce in vivo animal and human studies discussing the clinical and biological outcomes of the AgNPs.

Recently, the European Federation of Periodontology (EEP) has proposed evidence-based guidelines for periodontal therapy (systemic antimicrobial adjuncts)[46] and recognized that the clinical outcomes of scaling and root planning could be significantly improved with the adjunctive use of systemic antimicrobials especially with a combination of amoxicillin and metronidazole. Although minor, the clinical guidelines also acknowledged that the antimicrobial combination (amoxicillin and metronidazole) was related to the most significant occurrence of side effects.[46] On the other hand, locally delivered subgingival antimicrobial (adjuncts to scaling and root planning), showed significant clinical improvements in pocket depth reduction and clinical attachment level without any side effects. With the introduction of the recent EEP clinical guidelines, it is expected that the adjunctive use of local and/or systemic antimicrobials in the periodontal therapy will be significantly increased. In this regard, due to the potential risk of antimicrobial resistance with contemporary antibiotics, unconventional therapeutic regimens that are safe and have high antimicrobial efficacy should be tried as an adjunct in the management of periodontal and peri-implant therapy. The presented review has limitations; some data was unavailable due to language restrictions. Hence, some relevant studies may have been missed. Most studies included in the review used small sample sizes and presented short-term results. This could influence the interpretation of the outcomes.

CONCLUSION

- Nano-biomaterials have transformed traditional medicine and are now considered an essential part of modern medicine.
- Silver and AgNPs in the prevention and or reduction of gram-positive and/or gram-negative bacteria have been successfully applied.
- The review identified that AgNPs had been successfully used to prevent or minimize the occurrence of periodontal and peri-implant infections.
- Although in vitro and in vivo small-animal studies have demonstrated the safety and antimicrobial efficacy of AgNPs in periodontal and peri-implant wound healing, its therapeutic potential in clinical situations has not been explored.
- This lack of confidence has been attributed to several factors, including inappropriate formulations of AgNPs, fear of adverse effects, and scarce translational research using adequate animal models.
- There is a need to establish animal models that are closer in soft and hard tissue response to humans to verify the in vitro outcomes and test the safety and efficacy of AgNPs.

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