Review Article
DOI: 10.22037/jds.v38i3.33836
ISSN 2645-4351

Emerging Trends of the Applications of Nanoparticles in Dentistry: A Literature Review

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(*Submitted: 27 January 2021 – Revised version received: 5 April 2021 – Accepted: 7 April 2021– Published online: Summer 2021*)

Objectives Microorganisms are the main culprits responsible for many oral conditions including dental caries and periodontal diseases. To increase the quality of dental treatments, we can produce dental materials with antimicrobial properties. Nanoparticles with their antimicrobial activities can help achieve this goal. The purpose of this study was to describe the applications of nanoparticles in different fields of dentistry.

Methods An electronic search was conducted in the PubMed and Google Scholar to find articles related to the applications of nanoparticles in dentistry. No limitations were set regarding the date of publication or the language. We selected 73 articles and summed up the information.

Results Nanoparticles can be effectively used in various fields of dentistry including prosthodontics, oral medicine, periodontics, implant therapy, bone augmentation, restorative and preventive dentistry, orthodontics and endodontics, as well as in dental office disinfectants.

Conclusion Incorporating nanoparticles into dental materials is the most common application of nanoparticles in dentistry, which leads to an increase in antimicrobial properties of dental materials. Cancer diagnosis and treatment, regeneration of alveolar bone defects, and treatment of tooth hypersensitivity are the other emerging applications of nanoparticles in dentistry.

Keywords Anti-Infective Agents; Nanoparticles; Dentistry; Nanotechnology; Nanostructures

Introduction

Nanoparticles are desirable in material science and biology because of their unique properties.[1, 2] Due to the size of these materials, nanomaterials exhibit special characteristics such as high surface-volume ratio and higher reactivity compared with bulk materials.[3] Nanoparticles with vast physicochemical and functionalization (ligand attachment) properties have antimicrobial activities and can confer antimicrobial activity and/or increase the activity of the conventional antimicrobial agents. The antimicrobial activity of nanoparticles is related to destruction of cell membrane, blockage of enzymatic pathways, and alterations of the microbial cell wall and pathways of nucleic materials.[4]

Dental biofilm is formed on solid surfaces including teeth, restorations, orthodontic appliances, or obturators.[5] Several conditions such as impaired homeostasis of biofilm and excessive growth or proliferation of acidogenic bacteria may lead to dental caries and periodontal disease. Also, presence of bacteria in the root canal system causes complications and failure of root canal treatment.[6] Nanomaterials can help overcome many of these limitations in different fields of dentistry.

Materials and Methods

Two electronic databases namely the PubMed and Google Scholar were searched for this literature review. No limitation was set in language, and the search was conducted from the earliest publication until January 2021 using the following search terms: "Nanoparticle" and "Dentistry", "Prosthodontics" and "Nanoparticle", "Oral disease" and "Nanoparticle", "Oral medicine" and "Nanoparticle", "Periodontics" and "Nanoparticle", "Mouthwash" and "Nanoparticle", "Toothbrush" and "Nanoparticle", "Dental implant" and "Nanoparticle", "Bone graft" and "Nanoparticle", "Restorative dentistry" and "Nanoparticle", "Endodontics" and "Nanoparticle", "Orthodontics" and "Nanoparticle", and "Antimicrobial" and "Nanoparticle".

We finally selected 73 articles and summed up the information.

Results

Prosthodontics

Dental impressions are in direct contact with the saliva, blood, and bacterial plaque, which contain pathogenic microorganisms. Contaminated impressions can cause cross-contamination among patients and dental staff. Various disinfectants are used for disinfection of impressions by spraying or immersion. However, these disinfectants may lead to dimensional changes in impressions. Dental impressions containing silver nanoparticles have shown antimicrobial activity with no change in their properties.[7, 8] High concentration of silver in dental impression materials has no toxicity because of its low percutaneous absorption and limited contact time with the tissues 7.

Denture soft liners are used to distribute the forces applied to the soft tissues during occlusal functions. Soft lining materials can intensify the growth and proliferation of microorganisms. Microorganisms initially adhere to the surface of soft liners and then penetrate into the material; thus, use of common disinfectants is not suitable for soft liners 9. Modifying the soft liners by silver nanoparticles can solve this problem.[9, 10]

Candida species are the main cause of denture stomatitis. Denture stomatitis is the inflammation of oral mucosa under the denture base. Because of the irregularities and the pores on the surface of the acrylic resin denture bases, the inner surface of the denture can serve as a reservoir for microorganisms. To prevent biofilm formation, different mechanical and chemical methods are used for denture hygiene. Chemical disinfectants can change the mechanical and physical properties of the denture base resin. An in vitro study showed that chitosan nanoparticles decreased the number of colony forming units of candida species and made smaller changes in surface roughness and hardness of the material, compared with sodium hypochlorite, which is the most commonly used denture disinfectant. [11]

Polymethyl methacrylate (PMMA) is the most commonly used material as denture base in the fabrication of removable dentures, implant-supported prostheses, and intraoral maxillofacial prostheses. PMMA is susceptible to biofilm formation due to its features including the absence of ionic charge in methyl methacrylate resins, hydrophobic interactions, electrostatic interactions, and enhancement of mechanical bacterial attachment. Adding different antimicrobial agents to PMMA can overcome this limitation. Incorporation of nanoparticles such as TiO2 and silver nanoparticles in the formulation of PMMA can increase its antimicrobial and particularly antifungal properties.[12]

Yttria-stabilized zirconia (YSZ) is a popular dental material in restorations, implant abutments, and implant fixtures. YSZ has optimal mechanical properties and biocompatibility; however, biofilm formation mechanisms and secondary caries may lead to zirconia crown failures. Yamada et al. showed the optimal antibacterial effects of silver nanoparticle-coated YSZ against Staphylococcus aureus, Streptococcus mutans, Escherichia coli, and Aggregatibacter actinomycetemcomitans. The mechanism of its bactericidal action is contact killing, not releasing silver ions.[13]

<u>Oral medicine</u>

Oral cancer is one of the aggressive cancers with a high recurrence rate. For cancer prevention and disease management, early detection and diagnosis are important.[14] Despite the early diagnosis and treatment, the 5-year survival rate of the advanced stage of oral cancer is lower than 63%.[15]

The gold standard for oral cancer diagnosis is tissue biopsy, which is an invasive procedure. The traditional noninvasive diagnostic approaches including vital staining, exfoliative cytology, and molecular imaging have low specificity and sensitivity. In the field of oral cancer diagnosis, nano-based diagnostic methods are used such as molecular targeted imaging and biomarker analysis at nano-scale, which enable intraoperative identification of surgical resection margins, and control oral cancer prognosis after treatment.[14]

The treatment of squamous cell carcinoma as the most common oral cancer includes chemoradiotherapy and surgery. Such treatment options lead to non-specific death of cells. Nano-engineered systems can reduce non-specific cell death and increase the efficacy of therapeutic agents. Different types of nanotechnology-based carrier systems are considered for treatment of squamous cell carcinoma such as polymeric nanoparticles, polymeric micelles, nano-emulsions, layered nano-emulsions, nano-liposomes, solid lipid nanoparticles, nano-lipid carriers, cyclodextrin complexes, hydrogels, metallic nanoparticles, nanocarbon tubes, and receptor-mediated drug delivery systems.[16]

Radiological accidents cause radiological injuries alone or in combination with thermal, chemical, or physical trauma. Radiation combined injuries are life-threatening conditions with high mortality. One in vivo study showed that nanosilver could effectively heal the radiation combined ulcers by its anti-inflammatory property, enhancement of re-epithelialization, and fibroblast activation effects.[17]

Mouth dryness is a disorder that occurs due to factors that decrease the saliva flow. Artificial saliva is prescribed for mouth dryness. It should have special characteristics such as antibacterial properties. One in vitro study showed that incorporating core-shell magnetic nanoparticles in artificial saliva increases its antibacterial activity without influencing its rheological and physicochemical properties.[18]

<u>Periodontics</u>

Periodontitis is a chronic inflammation caused by the microorganisms of the subgingival biofilm. Elimination of pathogenic microorganisms of the biofilm is the main goal of periodontal therapy. Supra- and subgingival mechanical debridement in conjunction with various antiseptic agents is used for treatment of periodontitis.[19]

Chlorhexidine is a common antimicrobial agent that is used in various formulations in dentistry. Mesoporous silica nanoparticle-encapsulated pure chlorhexidine has great antimicrobial activities against oral pathogenic bacteria and can be used for clinical applications as a novel antimicrobial agent.[20]

Mouthwashes containing metal nanoparticles have great antibacterial effects against oral microorganisms. In vitro studies showed that mouthwashes containing nanoparticles had greater antibacterial effects than chlorhexidine. [21, 22]

Regeneration of intrabony defects in periodontal disease is difficult because of the complexity of periodontal tissues. The interactions between the local stem cells and immune cells can modify the regenerative processes.[23] For tissue regeneration, it is important to regulate the inflammatory responses and differentiation of periodontal cells. Au nanoparticles act as an anti-inflammatory agent by regulating cytokine production and modulating macrophage polarization. In one in vitro study, 45 nm Au nanoparticles caused an increase in newly-formed periodontal attachment, bone, and cementum in periodontal defects, and decreased tissue destruction. [24] Another study showed that human β-defensin3 combined with Au nanoparticles promoted osteogenic differentiation of human periodontal ligament cells in an inflammatory condition.[25] Nanoparticles can be used in toothbrush heads to enhance their antibacterial properties. In a randomized clinical trial, silver-coated toothbrush bristles decreased or maintained the low level of periodontal pathogens after 4 weeks of brushing.[26]

Implant therapy and bone augmentation

Alveolar ridge resorption or sinus pneumatization necessitate bone augmentation procedures before implant placement.

Various techniques and different materials can be applied for bone augmentation. A large number of synthetic bone graft materials have been introduced to dentistry such as hydroxyapatite (HA), biphasic calcium phosphate ceramics, and beta-tricalcium phosphate. These materials act as a scaffold for remineralization by osteoblasts.[27]

Nano-HA is a favorable bone graft. Stacchi et al. compared bovine bone and nano-HA as a bone graft in a split-mouth design. Both of these materials resulted in a regenerated tissue composed of more than 1/3 of vital bone after 6 months of healing. Nano-HA could be used as a suitable graft material for bone augmentation.[28] Infection can decrease the success rate of bone augmentation surgery. Adding nanosilver to beta-tricalcium phosphate can prevent this problem. One study showed that a suspension containing beta tricalcium phosphate and nanosilver had great antibacterial activity against Aggregatibacter actinomycetemcomitans and Prevotella intermedia.[29]

Abbasi et al. examined the cytotoxicity of nano-HA for human oral epithelium in cell culture. The results showed that nanohydroxyapatite is a good biocompatible material, particularly in concentrations less than 0.05 mg/mL.[30]

In guided bone regeneration, barrier membranes prevent fibrous tissue ingrowth and bacterial infections, and also induce bone formation. A study showed that silver nanoparticle-coated collagen membrane exhibited antibacterial effects against Staphylococcus aureus and Pseudomonas aeruginosa. Therefore, this type of membrane can prevent infection after bone grafting procedures. It also has anti-inflammatory effects by reducing the release of inflammatory cytokines including IL-6 and TNF-alpha. Silver nanoparticle-coated collagen membrane induces the differentiation of mesenchymal stem cells into osteoblasts and guides bone regeneration.[31]

Biofilm formation around dental implants may lead to peri-implantitis. Implant surface modification is an effective solution to develop an antibacterial surface that can prevent biofilm formation.[32] Titanium surfaces are incorporated with various nanoparticles such as zinc oxide, hydroxyapatite, nanocrystalline silver, copper, and bismuth that exhibit antimicrobial activity.[33, 34] An in vitro study showed that a silver-loaded polydopamine-coated implant could retard the growth of Streptococcus mutans and Porphyromonas gingivalis.[32]

Good oral hygiene is necessary to preserve good peri-implant health. Prophylactic products and toothpastes that clean tooth surfaces may lead to contamination and abrasion of implant surfaces because of their organic components and silica microparticles, respectively. The use of implant paste containing nanocrystalline magnesium phosphate gel and hydrated silica nanoparticles can remove oral biofilm and organic contaminants from the surface of titanium dental implants, and can also protect titanium implants from abrasion.[35]

<u>Restorative and preventive dentistry</u>

Biofilm formation on composite resin restorations more commonly occurs compared with amalgam and glass ionomer restorations. Accumulation of bacteria on the surface of composite resin restorations may lead to secondary caries and periodontal disease. Various antimicrobial agents can be added to composite resins such as chlorhexidine, methacryloyloxydodecylpyridinium bromide and antibacterial monomers, and other antibacterial fillers. Nanosilver has strong antimicrobial activity and can be incorporated into dental restorative materials. A study showed that addition of silver nanoparticles to Z250 composite inhibited the growth of Streptococcus mutans and Lactobacillus on the surface of this composite.[36] Application of spherical nanoparticles of Ag/ZnO as filler can inhibit biofilm formation of Streptococcus mutans on composite restorations, and can be a novel restorative material with antimicrobial properties.[37]

One main problem with dental adhesive restorations is low durability of the adhesive system. The adhesive/dentin interface hydrolysis is caused by host-derived matrix metalloproteinases and cysteine cathepsins. These enzymes are activated at a low pH. Acid etching and release of lactate by cariogenic bacteria can trigger this process. Addition of ZnO/Cu nanoparticles to the universal adhesive systems can improve their antimicrobial properties and integrity of the hybrid layer, without jeopardizing their biological, adhesive, and mechanical properties.[38]

The occlusal surface of the teeth with pits and fissures is at risk of dental caries. Pit and fissure sealants can inhibit caries by physical blockage of the pits and fissures, and inhibition of the leakage of fermentable carbohydrates into the pits and fissures. Nanofilled flowable composites are recommended for sealing of pits and fissures of molars, because of their low microleakage.[39]

Glass ionomer cements (GICs) are widely used as dental restorative materials, but the failure of these materials often occurs because of poor mechanical properties and secondary caries 40. Adding antibacterial agents into the conventional GICs can inhibit secondary caries. Incorporating reduced graphene-silver nanoparticles, silver nanoparticles, and magnesium oxide nanoparticles into GICs can improve their antibacterial activity.[40-42]

Incorporation of polyacrylic acid-coated copper iodide nanoparticles into the glass ionomer-based materials can improve their antibacterial activity, decrease collagen degradation, and increase the longevity of adhesive restorations.[43] Incorporation of nano-sized apatite crystals into the GICs improves their mechanical properties such as stability, insolubility, and bond strength to the tooth structure, in addition to the release of fluoride and subsequent reduction of secondary caries.[44]

Fluoride toothpastes have a great role in prevention of dental caries. To enhance the anti-caries properties of toothpastes, inorganic phosphate salts are added to these products. Evidence shows that toothpastes containing nanoparticles such as 0.5% nano-sized sodium hexametaphosphate, and nano-sized calcium carbonate can have an additional remineralizing effect on carious lesions.[45, 46]

Tooth hypersensitivity is one of the most common complaints among patients. The treatments of this problem include home remedies such as the use of desensitizing dentifrices containing strontium chloride, calcium carbonate, sodium fluoride, or potassium salts, and dental office methods such as fluoride varnish, restorative resins, and laser therapy. One study showed that use of dentifrices containing nano-carbonate apatite and laser therapy were effective for treatment of dentin hypersensitivity. At the initial stages, laser had a superior desensitizing effect but dentifrices showed a more durable effect in clinical situations.[47]

Orthodontics

White spot lesions and dental caries following orthodontic treatment are major challenges encountered by dental clinicians. To overcome these problems, different antimicrobial agents such as chlorhexidine, enamel remineralizing agents including fluoride, and composite resins containing calcium phosphate nanoparticles can be added to the orthodontic adhesive. When photo-activated 7.5wt% cationic curcumin-doped zinc oxide nanoparticles are incorporated into the orthodontic adhesive, the cariogenic multispecies biofilm, and also the metabolic activity of microorganisms can be controlled.[48] Also, an orthodontic adhesive containing quaternary ammonium polyethyleneimine showed antibacterial activity against Streptococcus mutans without compromising the mechanical properties and biocompatibility of the adhesive.[49]

Resin modified GICs (RMGICs) are highly desirable as orthodontic cement because of their fluoride release potential; however, they cannot completely prevent the formation of white spot lesions around orthodontic brackets. Incorporating antimicrobial agents into RMGIs can increase their antibacterial activity to reduce the acidic biofilm.[50] RMGIs containing nanoparticles of calcium fluoride and dimethylaminohexadecyl methacrylate have strong antibacterial and remineralizing properties. Jianru et al. showed that this cement resulted in greater enamel hardness in comparison with commercial cements without compromising the biocompatibility or orthodontic bracket-enamel shear bond strength.[51] One solution to prevent white spot lesions is the application of nanosilver-coated orthodontic brackets. This type of bracket can reduce Streptococcus mutans and dental caries.[52]

Friction between orthodontic wire and bracket is a hazardous factor against orthodontic movement.[53, 54] Any reduction in friction can accelerate tooth movement in the sliding technique and lead to better control of anchorage. One way to decrease this factor is coating of the porcelain bracket surfaces with ZnO nanoparticles.[53]

Endodontics

The goal of endodontic treatment is to preserve the health and functionality of natural teeth.[55] Microbial biofilm is the main cause of root canal infection.[56] A successful root canal therapy depends on removing the bacteria from the root canal system and prevention of re-infection of the root canal system. Root canal instrumentation is the most important step in endodontic treatment but it only debrides 70% of the radicular space; therefore, the main reason for mechanical instrumentation is enhancement of the effectiveness of root canal irrigation. Irrigation leads to mechanical washing and lubrication, dissolution of the remaining pulp tissue, and killing of microorganisms. Different irrigants are available, but none of them has ideal properties.[57]

Enterococcus faecalis is one of the frequent microorganisms that causes the failure of root canal therapy. It can penetrate into the dentinal tubes and survive in the process of chemomechanical preparation. Metal oxide nanoparticles can play an antimicrobial role against endodontic pathogens. Monzavi et al. showed that nano-MgO had longer efficiency for elimination of Enterococcus faecalis from the root canal system without cytotoxic effects in vitro.[58] Chlorhexidine hydrochloride is one of the recommended root canal irrigants due to its broad-spectrum antibacterial effect, sustained action, and low toxicity. To increase the penetration ability and antibacterial effects, newly formulated chlorhexidine hydrochloride nano-emulsion can be applied to irrigate the root canal system. One study compared the antibacterial efficacy of chlorhexidine hydrochloride nano-emulsion and the conventional chlorhexidine hydrochloride, and showed that chlorhexidine hydrochloride nano-emulsion had higher cleansing ability and antibacterial effect on Enterococcus faecalis, and resulted in great reduction or complete eradication of bacteria.[59] Studies that compared the antibacterial activity of nanosilver solutions and NaOCl as root canal irrigants showed that NaOCl had greater antimicrobial activity against Enterococcus faecalis.[60, 61] Tooth discoloration is a major problem after root canal therapy. Moazami et al. demonstrated that nanosilver materials could not be used as a root canal irrigant because they cause tooth discoloration.[62] De Almeida et al. compared Enterococcus faecalis anti-biofilm effects of conventional irrigants, ZnO nanoparticles and silver nanoparticles. The results showed that nanoparticle solutions had similar antibacterial effects to conventional endodontic irrigants. In their study, 2% chlorhexidine was the most effective on Enterococcus faecalis biofilm.[63]

Endodontic sealers are used to fill the irregularities between the root canal walls and to infiltrate into the dentinal tubules. Most root canal sealers have antibacterial activities although these properties decrease after setting. To overcome this limitation, various antibacterial agents can be added to the sealers. In one study, a sealer containing 5% dimethylaminohexadecyl methacrylate and 0.15% silver nanoparticles showed great antibacterial effects without compromising film thickness or sealing properties 64. When Tubliseal and AH Plus sealers are combined with chitosan nanoparticles and chlorhexidine, they exhibit the highest anti-microbial activity.[65]

Gutta-percha (GP) is the most common root canal filling material. It is malleable, inert, and biocompatible. However, it has several limitations including leakage, root canal re-infection, and poor mechanical properties. One study evaluated the use of nano-diamond embedded GP that was functionalized with amoxicillin as root canal filler. In comparison with unmodified GP, it showed improved mechanical properties. By removing the microorganisms from the root canal system, GP cones with amoxicillin-loaded nano-diamonds may improve the success of treatment.[66]

To decrease the number of bacteria in the root canal system between endodontic appointment sessions, intracanal medicaments such as calcium hydroxide are used. The microorganisms present in biofilms are more resistant to disinfection methods. To improve the antibacterial activity of calcium hydroxide, various antibacterial vehicles are added to it, such as chlorhexidine and silver nanoparticles. The mixture of calcium hydroxide and silver nanoparticles is the most effective against Enterococcus faecalis in comparison with chlorhexidine and saline.[67] Also, nanoparticulate calcium hydroxide has more penetration depth into the dentinal tubes compared with the conventional type.[68]

Root end filling is crucial because it can seal the root canal system. Mineral trioxide aggregate (MTA) is a root-end filling material. MTA has low antimicrobial effects. One study showed that combination of silver nanoparticles with MTA and a new experimental cement improved the antibacterial activities of these cements.[69]

Dental office disinfectants

Aerosols which are produced by dental instruments connected to dental unit waterlines may be contaminated with microorganisms and this could be a potential risk for transmission of infectious agents among patients and dental staff.[70] Abbasi et al. showed that dental unit water was contaminated with Gram-positive bacilli, Gram-positive cocci, and Gram-negative bacilli. Several methods are proposed to control this contamination.[71] Nanomaterials can be used as dental unit waterline disinfectant due to their antibacterial activity. Studies showed that silver nano-emulsion and nanoparticles affected dental unit waterline biofilms.[3, 72]

Deconex is one of the most commonly used disinfectants in dental offices for decontamination of surfaces and equipment. Deconex containing silver nanoparticles is an effective disinfectant for dental clinics and has higher antibacterial activity against Pseudomonas aeruginosa compared with plain Deconex.[73]

Discussion

Nanomaterials have a lot of applications in dentistry because of their antibacterial properties and regenerative features. This review mainly focused on antibacterial uses of nanoparticles when added to dental materials.

Adding nanoparticles to dental materials can lead to an increase in antibacterial properties. Also, for materials with inherent antibacterial properties, their antibacterial activities can be improved by reducing the size of particles to nanometer scale, and increasing the surface-to-volume ratio.

Microorganisms are the main cause of many oral conditions such as caries, periodontal disease, and root canal infections. Thus, production of dental materials with antibacterial properties will improve the outcome of dental treatments.

Nanoparticles are used for various purposes in different fields of dentistry. They can inhibit the transmission of infectious agents among patients and dental staff. Dental impression materials containing nanoparticles and dental unit waterline disinfectants are in this category.

The main purpose of incorporating nanoparticles into dental materials is inhibition of biofilm formation and improving the antibacterial activity of these materials. Incorporating nanoparticles into the denture soft liners, PMMA, YSZ, collagen membrane, titanium implant fixture, composite restorations, dental adhesives, GICs, and orthodontic brackets can effectively help us achieve this goal. Use of nanoparticles in antiseptic solutions such as chlorhexidine mouthwash and root canal irrigants can promote their antibacterial properties and biofilm eradication potential. Nanoparticles can also improve the mechanical properties of some dental materials such as GICs, dental adhesives, and orthodontic brackets.

Nanoparticles are also used in other fields of dentistry including diagnosis and treatment of cancer, regenerative processes, and bone grafting that were mentioned in this review, but not discussed in detail because the main purpose of this review was to address the antibacterial activities of nanoparticles.

Conclusion

Many oral diseases are caused by microbial agents that can cause dental caries, periodontal disease, and root canal infections.

Incorporating nanoparticles into dental materials increases their antimicrobial properties. Unlike antibiotics, nanomaterials will not lead to microbial resistance in the hosts.

Dental materials and products containing nanoparticles such as dental impression materials, mouthwashes, dental implants, restorative materials, and toothpastes can aid reduce the costs, failure rate, and re-treatment dental visits. Nanomaterials can also be used as disinfectants in dental offices to decontaminate the dental unit waterlines. Extensive use of nanomaterials requires more randomized clinical trials. Further research should aim at production of nanoparticle-containing dental materials to improve the quality of treatments provided to patients.

Conflict of Interest

Non Declared■

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How to cite:
Armanfar M, Abbasi F. Emerging Trends of the Applications of Nanoparticles in Dentistry: A Literature Review. J Dent Sch 2021;38(3): 119-125