Anti-Caries Nanomaterials

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Caries is the most common and extensive oral chronic disease. Due to the lack of anti-caries properties, traditional caries filling materials can easily cause secondary caries and lead to treatment failure. Nanomaterials can interfere with the bacteria metabolism, inhibit the formation of biofilm, reduce demineralization, and promote remineralization, which is expected to be an effective strategy for caries management.

Keywords: anti-caries ; nanotechnology ; nanomaterials ; antibacterial ; remineralization

1. Introduction

Caries is one of the most important diseases, which has seriously threatened human oral health, and even the whole body, for a long time [1]. According to statistics associated with 328 major diseases from “The Lancet-Global Burden of Disease Study 2016, GBD”, the prevalence of permanent teeth caries was the highest [2]. Based on modern theory in caries etiology, the imbalance of oral flora could result in acid accumulation and lead to tooth demineralization, inducing the caries formation. At present, caries treatment is still based on filling restoration. However, clinical studies showed that dental filling and bonding materials’ lack of anti-caries properties could result in a high incidence of secondary caries. The five-year failure rate in filling restoration is up to 50%. The replacement of restorations caused by filling failure leads to many public health resources waste. Therefore, the development of new anti-caries materials is a hot spot in the field of caries prevention and treatment.

Given the current problems and challenges in caries prevention and treatment, anti-caries nanomaterials have become a breakthrough in caries research. Nanotechnology was first proposed by Richard Feynman, which is a technology that studied the properties and applications of materials in the range of 1–100 nm. Nanomaterials are superior to traditional materials due to their physical/chemical advantages, such as volume effect, surface effect, quantum size, quantum tunnel, and dielectric confinement [3]. At present, the nanoparticles used include nanorings, nanopores, nanotubes, carbon, nanocapsules, nanospheres, and dendrimers [4]. Nanoparticles can be combined with polymers or coated on different biomaterials. The smaller the diameter of nanoparticles, the larger the specific surface area, and the stronger mechanical properties and antibacterial effect [5]. They can be used as the carrier of antibacterial drugs since nanoparticles have the characteristics of targeting antibacterial with the least side effects on the host. At present, a variety of antibacterial mechanisms of nanoparticles have been proposed, including metal ion release [6], oxidative stress [7], and non-oxidative mechanisms [8]. It is widely believed that the positively charged nanoparticles are attracted to the negatively charged cell membrane of bacteria by static electricity, which changes the permeability of the cell wall, leading to cell membrane rupture and organelle leakage.

2. Metal Nanoparticles Used in Caries Infections

2.1. Silver Nanoparticle (NAg)

Silver has a broad spectrum of antibacterial properties, which can inactivate enzymes and prevent DNA replication in bacteria. NAg further increases surface area ratio, making silver particles smaller and antibacterial effects better. When NAg was added to the adhesives, its antibacterial property increased significantly, but whether it had any effect on the bonding strength is still controversial. Some scholars have found that the antibacterial effect of NAg increased in a dose-dependent manner from 0.05%~0.1% with no effect on bonding strength or color [9]. However, ElkassasDW et al. [10] indicated that self-etching adhesive containing 0.05%~0.1% NAg can affect the bonding strength at pH 2.7. Cheng et.al [11] demonstrated that 0%~0.175% of NAg composite resin can significantly reduce biofilm growth and metabolic activity, in which antibacterial activity increased in a dose-dependent manner. Moreover, when the mass fraction of NAg is 0%~0.088%, the flexure strength and elastic modulus of modified composite resin are not significantly different from the control group. However, the flexural strength of modified composite resin decreased significantly when the nano-silver mass fraction was higher than 0.175% [12]. Mohadese Azarsina examined the antibacterial activity of NAg added in Z250 composite. The results showed that NAg could significantly inhibit the growth of Streptococcus mutans and Lactobacillus on the composite surface [13]. NAg can be released slowly from the materials and has good biocompatibility in a certain concentration range [14].

In recent years, NAg has been added to the resin in cooperation with other antibacterial agents, which has a good antibacterial effect against caries-related bacteria . In other research, Shenggui Chen et al. studied the antibacterial effect of polymethyl methacrylate (PMMA)-cellulose nanocrystals (CNCs)-NAg modified resin against Staphylococcus aureus and Escherichia coli. The authors concluded that PMMA-CNCs-NAg modified resin exhibited excellent mechanical properties, desirable biocompatibility, and excellent antibacterial activities [14]. Fang Li et al. found that the novel antibacterial adhesives containing quaternary ammonium dimethacrylate (QADM) and NAg are promising anti-caries nanomaterials. QADM and NAg can be used as antibacterial agents on the resin surface with good bacteriostatic effect [15]. In vitro artificial enamel caries model, reduced graphene oxide-silver nanoparticles (rGO/NAg) composite showed shallower lesion depth and less mineral loss compared with the control groups [16]. In the artificial dentine caries model, Irene et al. found that polyethylene glycol-coated silver nanoparticles (PEG-NAg) can remineralize dentine caries and inhibit collagen degradation without causing significant tooth staining [17]. In the rat caries model, NAg coated orthodontic brackets inhibited Streptococcus mutans for 30 days and reduced caries on the smooth surfaces [18].

2.2 Nano-Zinc (NZn) and Nano-Zincoxide (NZnO)

NZn has a wide antibacterial spectrum, which antibacterial ability mainly comes from the quantum size effect of dissolving and releasing zinc nanoparticles. Matrix metalloproteinases (MMPs) can be activated in both total-etch and self-etch adhesives, which induce degradation of resin and dentin matrix, shortening the service life of adhesives. NZn can reduce the expression of MMPs and prolong the lifespan of adhesive. It has been reported that the addition of Zn^{2+} to total-etch adhesive can inhibit MMPs activity, reduce the decomposition of dentin collagen bundle, and protect mineral crystal formation at the eosin–tooth interface, improving the nano-mechanical properties [19][20]. Compared with micron ZnO, NZnO has higher surface potential energy and can release more zinc ions to kill bacteria. Besides, some scholars believed that NZnO could also activate the photocatalytic antibacterial mechanism and produce a large number of free radicals to interact with bacteria [21]. Tavasoli et al. [22] studied 0–5% NZnO composite resin and found that 1% NZnO had no obvious effect on the mechanical properties of the composite resin. With the increase of mass fraction (0–5%), the number of *Streptococcus mutans* was decreased significantly in 24 h [23]. NZnO has been added to resin or binder alone or in cooperation with other antibacterial agents. As recent researches asserted the antimicrobial effects of NZnO and chitosan (CS) nanoparticles, which results demonstrated that the two components of nanoparticles in the composite resin can be synergistically beneficial in reducing the number of microorganisms [24]. Yazi Wang et al. explored the mechanical and antibacterial properties of cellulose nanocrystal/zinc oxide (CNC/ZnO) nanohybrids of the dental resin composites [25]. They concluded that CNC/ZnO nanohybrids positively affected the mechanical and antibacterial properties on dental composite resin which are promising to resist secondary caries. In the dentine caries model, Mario et al. found that NZnO and copper nanoparticles (NCuO) addition in universal adhesive systems provided antimicrobial, anti-MMP activities and improved interface stability on caries-affected dentin [26].

2.3. Other Metal Nanoparticles

TiO_2 nanoparticles ($NTiO_2$) were incorporated into glass-ionomer at 3% and 5% (*w*/*w*), exhibiting an antibacterial activity in direct contact test against *Streptococcus mutans* [27][28]. Moreover, *N*TiO_2-containing dental adhesives (80% *v*/*v*) had strong antibacterial efficacy against *Streptococcus mutans* biofilms [29] with good biocompatibility [30]. In vitro experiment, an acrylic resin containing $NTiO_2$ (0.5%) and nano-SiO_2 ($NSiO_2$, 1%) in acrylic liquid reduced the cariogenic bacterial count (*Lactobacillus acidophilus and Streptococcus mutans*) by 3.2–99% in a time-dependent manner [31]. Toodehzaeim MH et al. indicated that incorporating NCuO into adhesive (0.01, 0.5, and 1 wt.%) added antimicrobial effects to the adhesive with no adverse effects on shear bond strength [32]. Besides, the incorporation of Cu nanoparticles into adhesive renders the adhesive antibacterial to *Streptococcus mutans* for at least 1 year [33][34]. The MgO nanoparticles (NMgO) modified glass-ionomer cement showed effective antibacterial and antibiofilm activity against two cariogenic microorganisms (*Streptococcus mutans* and *Streptococcus sobrinus*) [35].

3. Quaternary Ammonium Salt Polyethylenimine (QAS-PEI) Nanoparticles

QAS is a highly active cationic agent with a wide antibacterial spectrum [38][39]. QAS-PEI nanoparticles were prepared based on polyethyleneimine cross-linked structure which makes the modified composite with high chemical stability and antibacterial properties under different oxidants and storage conditions, without effect on the oral micro ecological balance. The antibacterial mechanism of QAS-PEI is related to the electrostatic interaction between positively charged QAS-PEI and negatively charged bacterial cell walls [40]. QAS-PEI nanoparticles incorporated in resin-based composite at

2% wt/wt have demonstrated prolonged inhibition of bacterial growth [41]. Yudovin Farber et al. [42] added 1% QAS-PEI nanoparticles into the composite resin. Through 3 months of long-term experiments in vitro, it was confirmed that the composite resin had strong sustained antibacterial activity against Streptococcus mutans, and the alkyl chain length of polyethyleneimine had a significant influence on the antibacterial effect. In addition, some scholars have added QAS-PEI nanoparticles into glass ionomer polymer and found it has an obvious antibacterial effect on Streptococcus mutans and Lactobacillus [43]. Moreover, Nurit Beyth et al. investigated the biocompatibility of QAS-PEI nanoparticles incorporated in a resin composite [44], revealing that TNFα secretion and macrophage viability were not altered by QAS-PEI nanoparticles.

4. Biomimetic Nanocatalyst

The application of nanocatalyst is a new approach to combat cariogenic plaque-biofilm in nanotechnology. In a previous study, catalytic iron oxide nanoparticles (CAT-NP) have been shown exceptional topical anti-biofilm effects in vitro [45]. Moreover, CAT-NP/H2O2 was observed to suppress the onset and severity of dental caries in vivo in a rodent model [45]. With an in-depth study, Pratap C. Naha et al. reported that dextran-coated iron oxide nanoparticles termed nanozymes (Dex-NZM) displayed strong catalytic activity at acidic pH values and targeted biofilms with high specificity, preventing the development of dental caries in a pH-dependent manner in vivo [46].

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