Narrative Review

Dental restorative materials containing quaternary ammonium compounds have sustained antibacterial action

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ABSTRACT

Background. This narrative review addresses dental restorative materials with sustained antibacterial action, especially those containing quaternary ammonium compounds. Secondary caries occurs around restorations, causing further loss of mineral and breakdown of the restoration. Lesions adjacent to restorations account for more than 40% of needed restorations. Restorative materials with antibacterial properties will potentially solve this problem.

Types of Studies Reviewed. Several groups are researching composite restorative materials that incorporate antibacterial agents. These agents are mostly exhausted over time. Newer studies involve materials that incorporate antibacterial microparticles that remain active and do not leach out.

Results. One such antibacterial agent, quaternary ammonium coupled with inorganic silica into minute particles (QASi), has been studied in the laboratory and in humans. QASi particles incorporated into dental materials retain their antibacterial action over time without leaching or loss of activity. A clinical in situ study in humans using dental composite containing QASi resulted in highly significantly less demineralization in the adjacent enamel than the control composite material.

Conclusions and Practical Implications. Dental restorative materials that contain QASi have sustained antibacterial properties, have mechanical properties comparable to those of presently marketed materials, and have been cleared by the US Food and Drug Administration. Clinical studies have shown that composites incorporating QASi have the potential to markedly reduce the occurrence of caries around restorations. Because caries around restorations is a major problem, restorative materials with sustained antibacterial properties will have an important effect in reducing secondary caries around restorations.

Key Words. Caries prevention; antibacterial restorative materials; secondary caries; quaternary ammonium compounds.

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CARIES MANAGEMENT AND THE NEED FOR MINIMAL INTERVENTION DENTISTRY

Caries is bacterially generated and the so-called cariogenic bacteria, which include mutans streptococci, *Lactobacillus* species, and bifidobacteria, generate acids when they metabolize fermentable carbohydrates ingested by humans.[1,2] These acids dissolve the tooth mineral (enamel, dentin), leading to cavities if the process is not halted.[1,3] The progression or reversal of caries is determined by the balance between pathologic factors (bacteria, carbohydrates, lack of saliva) and protective factors (saliva, fluoride, remineralization, antibacterial action), depending on which of these 2 groups of factors prevail.[3] When restorations are placed to fill cavities they do not reduce bacteria in the rest of the mouth, and generally caries continue to progress unless other measures are taken, including remineralization (enhanced by fluoride) and antibacterial therapy.[1,4-7]

Secondary caries

So-called secondary caries occur around restorations, causing further loss of enamel or dentin mineral and breakdown of the composite restorations. This topic has been reviewed by several authors.[8-10] Mjör and Toffenetti[8] concluded that "secondary caries is the same as primary caries

located at the margin of a restoration." Carious lesions adjacent to restorations account for more than 40% of restorations that are needed due to caries.[10] Therefore, prevention or reversal, or both, of secondary caries should be thought of similarly to caries in any other region of the tooth. If a restoration is needed as a result of cavitation due to caries, every measure possible should be taken to inhibit or stop the recurrence of caries around the restoration.

Caries management and secondary caries

The management of caries by risk assessment is now well established.[11-15] Patients with existing caries, recent restorations owing to caries, or both, are at high risk for new caries. Continuing carious activity around restorations is bacterially generated and leads to the breakdown of the surrounding dentin or enamel and the composite restoration. This is a major problem that requires a solution.[10] Minimal intervention dentistry (also known as minimally invasive dentistry) calls for remineralization and antibacterial therapy[12,16] and the minimal use of appropriate restorative therapy. Fontana and Gonzáles-Cabezas[9] in their review of secondary caries concluded that "although secondary caries is still the main reason for restoration replacement, the development of new technologies for detecting and monitoring these lesions at an early stage should allow for testing new interventions to arrest or remineralize these lesions, which would delay the need for re-restoration." The same reasoning applies to the use of restorative materials with long-term antibacterial properties. Long-term antibacterial activity would allow for ongoing inhibition of demineralization, arresting the progress of the lesion and enabling remineralization. The commercial availability of composite restorative materials with long-term antibacterial properties is therefore a major unfilled need in the world of minimal intervention dentistry.

DENTAL MATERIALS WITH ANTIBACTERIAL PROPERTIES

Composite Dental Restorative Materials

Carious regions of enamel and dentin are most likely to be repaired clinically using composite resin materials. The mechanical properties of composites have improved substantially over the years since they were introduced into dentistry. However, placing such restorations does not take care of the caries-related bacteria in the remainder of the mouth. These bacteria readily form new plaque on the composite surface, often leading to recurrent caries around the restoration, as described previously.[8-10]

Composite Dental Restorative Materials That Release Antibacterial Components

Several investigators have reported studies on composite materials that include antibacterial components released over time.[17] Chen and colleagues[18] reviewed reports of such materials. Antibacterial compounds in their review fell into 3 categories: (1) leachable compounds such as benzalkonium chloride and chlorhexidine, (2) polymerizable monomers such as quaternary ammonium (QA) methacrylates, and (3) filler particles such as nanosilver. Although numerous antibacterial compounds were studied in the review period from 2012 through 2017, commercial products incorporated only 4 agents, namely, benzalkonium chloride, chlorhexidine, glutaraldehyde, and 12-methacryloyloxydodecylpyridinium bromide. The release of these agents over time resulted in loss of activity and weakening of the remaining composite material as well as discoloration. There is, therefore, a need for a composite restorative material that incorporates an antibacterial agent that is not released but retains its antibacterial activity over time.

ABBREVIATION KEY

ABR: Antibacterial imidazolium-containing resin.
ABR-MC: ABR-modified methacrylate-based composite.
QA: Quaternary ammonium.
QPEI: Quaternary ammonium polyethylenimine.
QASi: Quaternary ammonium silica.

Composite Dental Restorative Materials That Incorporate Nonleaching Antibacterial Components

Several groups are conducting research regarding composite restorative materials that incorporate antibacterial components that are not released over time.[17,19-21] The concept is that the antibacterial component retains its antibacterial action even though covered with dental plaque in the mouth. The purpose of this article is not to review all the studies that have been published or to review all those that are in progress, but rather to highlight a few that represent progress toward clinical reality, especially those describing QA compounds. Almost all of the published reports are laboratory studies, often with promising results. However, the reality of efficacy in the human mouth is the key to clinical usefulness and to major reductions in secondary caries. The emphasis of this

narrative review is on investigations that have led to successful clinical applications or are likely to in the future.

Composite Dental Restorative Materials That Incorporate Antibacterial Components Other Than QA Compounds

A research group at the University of Pennsylvania has reported laboratory studies on a new composite that incorporates a nonleachable antibacterial compound. This composite has potent antibiofilm activity. The material combines a polymerizable antibacterial imidazolium-containing resin (ABR) with a methacrylate-based modified composite (ABR-MC).[22] Inclusion of the ABR moiety at about 2% provided bioactivity with minimal cytotoxicity and without compromising the mechanical integrity of the composite. A *Streptococcus mutans* biofilm model was used to assess the antibiofilm properties of ABR-MC. ABR-MC altered the biofilm architecture by impairing the ability of *S mutans* to form organized bacterial clusters on the surface in contrast to the control composite on which a resilient biofilm formed. The mechanical properties of the composite were not compromised by incorporation of the antibacterial component. These laboratory studies show the potential of this new nonleachable antibacterial composite to inhibit recurrent caries around restorations.[22] In vivo and human clinical studies are yet to be reported.

A 2021 report described a comprehensive laboratory study examining a novel resin that incorporates both antibacterial and remineralizing components.[23] The authors developed a low-shrinkage, antibacterial, and remineralizing nanocomposite. The resin that this group developed contains urethane dimethacrylate, triethylene glycol divinylbenzyl ether, 3% dimethylaminohexadecyl methacrylate, and 20% nanoparticles of amorphous calcium phosphate. Using a laboratory model, they showed that antibacterial properties were maintained over several months in an acid environment that included a biofilm. This material is promising, but at this stage only laboratory data are available.

Composite Dental Restorative Materials That Incorporate QA Compounds

QA compounds have been used for decades as potent antimicrobial agents for several purposes including food packaging and biomedical applications.[24] Much research has been devoted to the search for QA compounds with optimum antimicrobial action for the desired purpose. For an optimum effect in dental materials, research suggests that the chain length of the QA compound be 12 to 16 carbon atoms.[21,25] A systematic review by Makvandi and colleagues[21] detailed articles that dealt with QA compounds relevant to dental materials. QA compounds can be incorporated into dental composites in 2 main ways: (1) polymerized as a QA monomer or (2) added as a QA component of a filler.

Laboratory studies on numerous promising compounds that fall into the category of a QA compound as a monomer were reviewed by Makvandi and colleagues.[21] For example, Liang and colleagues[25] studied a series of QA dimethacrylate monomers in bisphenol A-glycidyl methacrylate/trimethylene glycol dimethacrylate dental resin systems for antibacterial activity with the aim of optimizing chain length and other aspects of the compounds involved. A laboratory study[26] published after the review by Makvandi and colleagues[21] reported work on copolymers based on QA urethane-dimethacrylate analogs and triethylene glycol dimethacrylate. The authors showed that the copolymers they produced had good physical properties as dental materials and that they had excellent antibacterial properties in laboratory models. Such polymers show promise as antibacterial dental materials of the future. Clinical studies are needed to confirm such promise.

QA compounds that are incorporated into dental materials as a filler can be based on materials that are combined with a filler such as silica or with a polymer such as QA polyethylenimine (QPEI). Both materials have been well researched in laboratory and clinical studies, as detailed below.

QPEI

One promising antibacterial agent is QPEI in the form of minute polymeric particles.[20,27-30] QPEI is formed when the potent antibacterial QA is polymerized to form minute particles. These particles can be incorporated into dental composites, cements, or sealants while retaining their antibacterial activity and not leaching out over time. Related dental research has been published on this material since 2006; key articles are reviewed below.

QPEI: Laboratory Studies

QA compounds have been used for decades, in solution, as antibacterial agents for many purposes. They are potent antibacterial agents. Research led to polymerization with materials that could form minute particles with antibacterial activity in solid form and act as a filler in dental materials. Work on more than 50 such compounds led to a thoroughly executed research project investigating QPEI polymeric particles that were incorporated into composite dental materials. The antibacterial properties of the resulting restorative materials were tested over time, together with the mechanical properties of the composites. One significant advantage of incorporating QA in this manner is that the material is dispersed throughout the dental material, and the antibacterial groups are therefore available on all surfaces even after processing, polishing, cutting, or fracturing.

Extensive studies were conducted in which QPEI particles were incorporated at 1% (wt/wt) into clinically used bonding, flowable, and hybrid dental composite resins.[20] The composite materials were tested for antibacterial efficacy and relevant mechanical properties. *S mutans* was used as the test species in a number of models to assess antibacterial activity. All 3 types of composites that included QPEI showed antibacterial activity over time (at least 1 month) in direct contact tests, diffusion tests, bacterial growth tests, and evaluation by scanning electron microscopy. The QPEI did not leach out. Complete inhibition of bacterial growth was shown in the 1-month-aged samples in these laboratory tests. The relevant mechanical properties of the materials were not compromised by the incorporation of QPEI particles.

A further exhaustive laboratory study was conducted by the same group to assess the effect of incorporated QPEI on the bacterially generated changes in composite materials, including surface roughness, over time.[28,29] Control composite resin without QPEI showed an increase in surface roughness over time after 1 month of bacterial challenge, whereas the material containing QPEI did not increase in surface roughness. *S mutans* growth over 6 months, as assessed by the direct contact method, was completely inhibited on composites containing QPEI. X-ray photoelectron spectroscopy was used to show that the QPEI particles remained available at the surface over time.

Demineralization (precavitated carious lesions) around orthodontic brackets has been an ongoing problem for decades. A Tel Aviv research group has evaluated an orthodontic cement that incorporates QPEI particles.[31] The QPEI particles were incorporated at 0%, 1%, and 1.5% (wt/wt). The material with 1.5% QPEI showed sustained antibacterial action against *S mutans* in the direct contact model over time. The sheer bond strength to enamel was not compromised by incorporation of the antibacterial material, nor was the degree of monomer conversion, nor was the biocompatibility with keratinocyte and neutrophil cells. Orthodontists should consider using dental materials that possess antibacterial properties in patients undergoing long-term fixed orthodontic therapy.

QPEI: In Vivo Studies

Further studies have been done to assess the antibacterial behavior in vivo of dental composite restorative materials that incorporate QPEI particles.[29] Composite resin blocks that incorporated 1% (wt/wt) QPEI particles were housed in removable acrylic appliances together with control blocks with no QPEI. These appliances were each worn in the mouths of 10 human volunteers for 4 hours to allow formation of intraoral biofilm. Biofilm vitality, as assessed by confocal laser scanning microscopy, was reduced by more than 50% ($P < .00001$) in the QPEI group. Furthermore, the biofilms on the material that incorporated QPEI showed a decrease in viable bacteria of 70% vs the control biofilms. The authors concluded that the antibacterial effects previously indicated in vitro by QPEI incorporated at low concentrations into composites were also observed in vivo, even after only a few hours of biofilm formation. The antibacterial effects observed in these in vivo experiments are relevant to multiple-species natural biofilms formed in human mouths.

It is likely that the antibacterial effects of these QPEI particles are also applicable if these particles can be impregnated into other materials used in health care. The same research group studied QPEI in wound dressings as used for patients with orofacial cancer.[32] Strong antibacterial activity was shown by these impregnated materials vs a wide variety of microorganisms. If such antibacterial results are sustained over time, this technology, by which the agent is not released, may have wide uses in health care. This in vivo study confirms that a large advantage of incorporating QA in this manner is that the QA is dispersed throughout the material and the antibacterial groups are therefore available on all surfaces.

QA Silica (QASI): Laboratory and Clinical Studies in Humans

Laboratory studies with QASi

QPEI was the first generation of QA insoluble antibacterial particles that were designed to kill bacteria on direct contact when incorporated into dental restorative materials. The early in vitro and in vivo studies described previously showed that these polymeric particles were potent contact-acting bactericides owing to the high concentration of QA groups that were exposed and available on the surface of the materials. The research group has now developed a second generation of particles that incorporate QA together with inorganic silica as the core with the same functional groups of QA exposed. The antibacterial properties of these new particles, known as QASi, are the same as those of QPEI, and the QASi particles do not leach out over time according to manufacturers Nobio (Moran Weisshof, vice president, Clinical Affairs, Nobio, written communication, February 1, 2022) and Eurofins Bio-Lab (via Moran Weisshof, vice president, Clinical Affairs, Nobio, written communication, February 1, 2022). QASi incorporated into dental materials has been shown to improve compatibility with the composition of resin-based dental materials and consequently to reduce its impact on the mechanical and esthetic characteristics that are important in restorative dentistry. QASi particles are incorporated into dental restorative materials at 1.5% wt/wt to best inhibit bacterial growth on the surfaces of these materials.

Dental materials incorporating QASi have been subjected to the same rigorous laboratory testing as QPEI particles and have shown excellent antibacterial properties in a laboratory study.[33] The results were comparable to previously published studies with QPEI, as summarized above.

Human studies with QASi

The essential question that needed to be answered was whether dental restorative materials incorporating QASi would provide antibacterial action over time in the mouths of humans and thereby inhibit demineralization and the progression of caries around restorations. A 2022 study provided in vivo results in a limited number of human participants.[33] The study showed marked inhibition of bacterial growth on QASi-containing composites in human mouths over 6 months.

A clinical study was conducted in 2021 by Rechmann and colleagues[34] to assess the efficacy of QASi in human mouths over time. The study compared a dental composite restorative material that incorporated QASi particles and other fillers with a control material that was a comparable dental composite without QASi in a split-mouth model. The lower removable partial dentures of 20 participants were modified to incorporate the QASi material in 1 acrylic flange and the control composite in a flange on the other side of the mouth. In each case, a slab of human enamel was placed next to the composite material but separated by a standardized gap of 38 μm to allow dental plaque to grow between the composite and the enamel. Each participant wore their appliance continuously for 4 weeks. At the end of the test period the enamel samples were removed and the degree of demineralization of the enamel slabs that were exposed to the plaque biofilm in the gap was measured in the laboratory by cross-sectional microhardness assessment. The level of demineralization in these caries-prone participants was inhibited by more than 70% ($P < .0001$) by the QASi incorporated into the composite restorative material. This in situ clinical study in humans showed that the restorative material that incorporated QASi particles maintained antibacterial activity over time and markedly inhibited demineralization of the enamel in human mouths.

CONCLUSIONS

Patients with existing caries, recent restorations owing to caries, or both, are classified as high caries risk, with the high likelihood of ongoing carious lesions. Continuing carious activity around restorations is bacterially generated and leads to the breakdown of the surrounding dentin or enamel and the composite restoration. This is a major problem that requires a solution. Restorative materials with long-term antibacterial properties will be a major contributor to solving this critical oral health problem.

Several antibacterial materials with the potential to have long-term efficacy when incorporated into dental materials are under investigation in laboratory studies. One group of such compounds is based on substrates that combine with QA. In laboratory studies, QPEI polymeric particles were shown to be highly effective antibacterial agents.[20,27,28,30,31] They inhibited breakdown of the composite, did not leach out, and maintained their antibacterial action over time. Limited in vivo

studies[29,32] have supported the laboratory studies by measuring biofilm accumulation and activity over 4 hours in human mouths and assessing bacterial viability. The QPEI caused cell death throughout the formed biofilm, not just at the restorative material surface.

The second generation of QA antibacterial compounds, in which QA is coupled with silica to form QASi particles, has shown comparable antibacterial properties in laboratory tests.[33] QASi can be incorporated into resin-based dental restorative materials at 1.5% without compromising the mechanical properties (Moran Weisshof, written communication). The QASi antibacterial particles are uniformly dispersed throughout the dental material, remain in place, and continue their action over time, eliminating the problems of leaching, loss of activity, unnecessary ingestion, and accumulation in the body and the environment (Moran Weisshof, written communication). A clinical study in humans has shown that QASi particles in composite restorations significantly reduce demineralization in enamel adjacent to these restorations.[34]

Dental restorative materials that contain QASi will potentially have a major effect in reducing secondary caries around restorations. Various dental restorative materials that incorporate QASi (Infinix; Nobio) have been cleared by the US Food and Drug Administration for use in humans for restorative purposes; a further clearance states that "the addition of the QASi particles to the Infinix™ [range of products] reduces demineralization, which is part of the caries-formation process."[35] These restorative materials have comparable mechanical properties to presently marketed materials and have been cleared by the US Food and Drug Administration for immediate use. The long-term positive benefits are potentially great, but we will only know how much as the use of these products becomes widespread. There is some evidence to support clinical use of dental restorative products that incorporate QASi in the everyday practice of restorative dentistry.

The marketing of such products will require extensive consumer (dentist) education but will be a major step forward in caries control and management worldwide.

At the same time as the use of these materials becomes common, restorative materials that incorporate QASi should be further studied in human mouths to verify long-term antibacterial efficacy, stability, and integrity of the composites. ■

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