

Remineralization of artificial dentinal caries lesions by biomimetically modified mineral trioxide aggregate

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ABSTRACT

Fluoride-releasing restorative materials are available for remineralization of enamel and root caries. However, remineralization of dentin is more difficult than remineralization of enamel due to the paucity of apatite seed crystallites along the lesion surface for heterogeneous crystal growth. Extracellular matrix proteins play critical roles in controlling apatite nucleation/growth in collagenous tissues. This study examined the remineralization efficacy of mineral trioxide aggregate (MTA) in phosphate-containing simulated body fluid (SBF) by incorporating polyacrylic acid and sodium tripolyphosphate as biomimetic analogs of matrix proteins for remineralizing caries-like dentin. Artificial caries-like dentin lesions incubated in SBF were remineralized over a 6 week period using MTA alone or MTA containing biomimetic analogs in the absence or presence of dentin adhesive application. Lesion depths and integrated mineral loss were monitored with microcomputed tomography. The ultrastructure of baseline and remineralized lesions was examined by transmission electron microscopy. Dentin remineralization was best achieved using MTA containing biomimetic analogs regardless of whether an adhesive was applied; dentinal tubules within the remineralized dentin were occluded by apatite. It is concluded that the version of MTA employed in this study may be doped with biomimetic analogs for remineralization of unbonded and bonded artificial caries-like lesions in the presence of SBF.

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1. Introduction

Minimally invasive treatment of deep dentin caries adjacent to vital pulps has been used in attempts to preserve caries-affected and even caries-infected dentin [1,2]. As caries is a dynamic process caused by an imbalance between demineralization and remineralization, fluoride-releasing restorative materials are used to restore the imbalance [3,4]. Although fluoride is not considered a common feature in naturally occurring biomineralization [5], its beneficial effects on enamel remineralization cannot be overstated. This applies especially to the improved dissolution resistance initiated by epitaxial deposition of fluorapatite over remnant apatite crystallites [6]. Nevertheless, remineralization of dentin with fluoride is more difficult to achieve than remineralization of enamel

[7]. While there are numerous studies showing that dentin remineralization is enhanced in the presence of fluoride [8,9], remineralization was only observed on the surface of etched enamel, not on the surface of etched dentin under the same remineralizing conditions [10]. This may be attributed to the paucity of apatite seed crystallites available for heterogeneous crystal growth [11].

Extracellular matrix proteins play critical roles in controlling apatite nucleation and growth in collagenous tissues [12]. Polycarboxylic acid biomimetic analogs of matrix proteins participate in recruitment of pre-nucleation clusters [13] to produce fluidic, polymer-stabilized amorphous calcium phosphate nanoprecursors [14]. These fluidic nanoprecursors infiltrate collagen fibrils and transform into intrafibrillar apatite using the fibrils as biomineralization templates [15]. Polyphosphates play an important role in the biomineralization of apatite [16]. Using polyacrylic acid and sodium tripolyphosphate as dual biomimetic analogs of matrix proteins, intrafibrillar apatite platelets were deposited in an ordered manner within collagen fibrils [17,18]. These results suggest that fluoride-free remineralization of the apatite-sparse surface of completely demineralized dentin may be achieved with biomimetic

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analogues of matrix proteins to overcome the thermodynamic energy barrier associated with homogeneous crystal nucleation [19].

Mineral trioxide aggregate (MTA) has found important applications in dentistry due to its biocompatibility and bioactive properties [20–22], among which is direct pulp capping [23]. The generic label “MTA” has been adopted for the different versions of mineral trioxide aggregate that are commercially available from different countries of origin. As the calcium silicate-containing material lacks phosphate, MTA becomes bioactive and produces apatite only when it comes into contact with phosphate-containing fluids [24–26]. Pulp-capping materials are often applied on caries-affected dentin. As indirect and direct pulp capping involves contact of restorative materials with phosphate-containing body fluids, calcium silicate-containing materials may be potentially employed for remineralization of dentinal caries in vital teeth. Although not currently included in its repertoire of clinical applications [23], it is envisaged that MTA may be modified for caries remineralization. Biomimetic mineralization of caries-like lesions has recently been reported with the use of Portland cement in the presence of polyacrylic acid and polyvinylphosphonic acid-containing simulated body fluid (SBF) [27] or polyacrylic acid and sodium tripolyphosphate-containing SBF [28]. While these studies provide the proof-of-concept that the procedure is an effective *in vitro* approach to more optimal remineralization of the mineral-sparse surface of a carious lesion, it is not possible to rely on dissolving biomimetic analogues in body fluids in a clinical setting. This necessitates the development of alternative approaches to translate the biomimetic remineralization strategy into a clinical delivery system. Moreover, Portland cement is not acceptable for clinical use due to its lack of radiopacity or the inclusion of potentially cytotoxic mineral elements [29]. Thus, the purpose of the present study was to determine if biomimetic analogues may be incorporated in MTA, a clinically acceptable, radiopaque Portland cement-based material for remineralization of artificial caries-like dentin. Specifically, as dentin remineralization with calcium phosphate resin cements is adversely affected by dentin adhesive application [30], the effects of dentin remineralization with biomimetic analogues-incorporated MTA in the presence or absence of dentin bonding were evaluated. The null hypothesis tested was that the dentin remineralization efficacy of MTA in SBF is not affected by the incorporation of biomimetic analogues or adhesive application.

2. Materials and methods

2.1. Preparation of artificial dentin caries lesions

Forty non-carious human third molars were obtained under a protocol approved by the Human Assurance Committee of the Georgia Health Sciences University. A 1 mm thick disk devoid of pulp exposure and remnant enamel over the surface of the exposed occlusal dentin was prepared perpendicular to the longitudinal axis of each tooth using a low-speed Isomet saw (Buehler, Lake Bluff, IL) under water cooling. The surface for creating the caries-like lesion was polished with 1200-grit silicon carbide paper to create a smooth surface. The opposing surface, together with the enamel rim and 1 mm of peripheral dentin of the polished surface (to serve as reference), was protected with varnish to limit the areas available for demineralization. A $280 \pm 20 \mu\text{m}$ thick layer of partially demineralized dentin was created on the uncoated surface by pH cycling [31]. The demineralizing solution consisted of 1.5 mM CaCl_2 , 0.9 mM KH_2PO_4 , 50 mM acetic acid and 5 mM NaN_3 adjusted to pH 4.8. The remineralizing solution consisted of 1.5 mM CaCl_2 , 0.9 mM NaH_2PO_4 , 0.13 M KCl and 5 mM NaN_3 adjusted to pH 7.0 with HEPES buffer. Each specimen was immersed in 10 ml of the demineralizing solution for 8 h followed by immer-

sion in 10 ml of the remineralizing solution for 16 h, with new solutions used for each cycle. This procedure was performed for 14 days at ambient temperature.

2.2. Microcomputed tomography

After pH cycling, each disk was sectioned to create a 4 mm wide slab containing the caries-like lesion. Each lesion was characterized non-destructively by microcomputed tomography using the method reported by Liu et al. [27] to determine the lesion depth and integrated mineral loss (ΔZ) across the entire 4 mm wide lesion. Briefly, the mineral profile of each artificial caries-like lesion was scanned under water using a SkyScan 1174 scanner (Micro Photonics, Allentown, PA, USA). A positioning jig was prepared for each specimen from a sectioned pipette tip. Low-viscosity polyvinylsiloxane impression material was injected into a sectioned pipette tip followed by insertion of a dentin slab to produce a slotted mold in which the slab could be covered with water during scanning (Fig. 1A). Precise fitting of the slab into the slotted mold enabled it to be removed from the jig for mineralization and to be reinserted into the same position for multiple microcomputed tomography scans. A 1 mm thick aluminum filter was placed in front of the detector to remove low-energy radiation from the polychromatic X-ray source. Scanning was performed with a spatial resolution of $6.28 \mu\text{m}$. Projection images were collected at 50 kV and 800 μA using 360° rotation, with 3 s exposure time per 0.6° projection step. Signal-to-noise ratio was improved by averaging of 30 frames. During the reconstruction phase using the NRecon software (Version 1.6.2), a 20% beam hardening correction was employed to reduce ring artifacts. After image reconstruction, two-dimensional (2-D) slices in the sagittal plane were acquired using Data Viewer and saved in a 256 grayscale format. The same parameters were used when the same slab was re-scanned during subsequent months.

Sagittal virtual serial sections derived from each slab were used to create a 2-D stacked image with CTAnalyzer. The stacked 2-D image was imported into ImageJ (NIH, Bethesda, MD, USA) to produce an overall mineral profile within a standardized volume of interest (VOI). A white vertical line was formed extending from the radiopaque, non-demineralized part of the slab surface to the radiolucent surface of the artificial carious lesion (Fig. 1B). This virtual line served as the superimposition reference for mineral

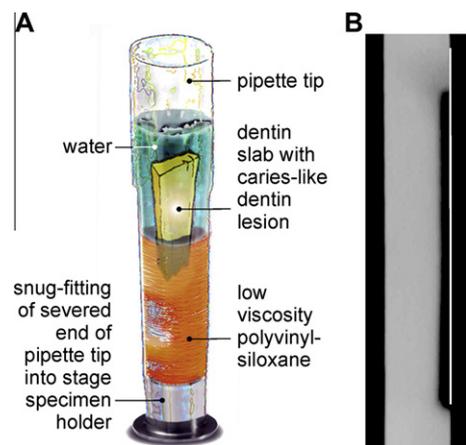


Fig. 1. Schematics of the methods employed in microcomputed tomography of artificial caries-like lesions. (A) Design of a specimen-specific positioning jig for repeated scanning of an artificial caries-like lesion under water to prevent dehydration during scanning. (B) Placement of a virtual line over the surface of a stacked image derived from multiple virtual sections obtained from microcomputed tomography for evaluation of the lesion depth and integrated mineral loss.

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