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Biomimetic remineralization of dentin

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ABSTRACT

Objectives. Remineralization of demineralized dentin is important for improving dentin bonding stability and controlling primary and secondary caries. Nevertheless, conventional dentin remineralization strategy is not suitable for remineralizing completely demineralized dentin within hybrid layers created by etch-and-rinse and moderately aggressive self-etch adhesive systems, or the superficial part of a caries-affected dentin lesion left behind after minimally invasive caries removal. Biomimetic remineralization represents a different approach to this problem by attempting to backfill the demineralized dentin collagen with liquid-like amorphous calcium phosphate nanoprecursor particles that are stabilized by biomimetic analogs of noncollagenous proteins.

Methods. This paper reviewed the changing concepts in calcium phosphate mineralization of fibrillar collagen, including the recently discovered, non-classical particle-based crystallization concept, formation of polymer-induced liquid-precursors (PILP), experimental collagen models for mineralization, and the need for using phosphate-containing biomimetic analogs for biomimetic mineralization of collagen. Published work on the remineralization of resin–dentin bonds and artificial caries-like lesions by various research groups was then reviewed. Finally, the problems and progress associated with the translation of a scientifically sound concept into a clinically applicable approach are discussed.

Results and significance. The particle-based biomimetic remineralization strategy based on the PILP process demonstrates great potential in remineralizing faulty hybrid layers or caries-like dentin. Based on this concept, research in the development of more clinically feasible dentin remineralization strategy, such as incorporating poly(anionic) acid-stabilized amorphous calcium phosphate nanoprecursor-containing mesoporous silica nanofillers in dentin adhesives, may provide a promising strategy for increasing of the durability of resin–dentin bonding and remineralizing caries-affected dentin.

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1. Introduction

Teeth are the most heavily mineralized tissues in the human body. Demineralization and remineralization processes coexist in teeth during the entire life of an individual. In pathological conditions, demineralization outweighs remineralization [1]. Fermentation of dietary carbohydrates by acidogenic bacteria results in the production of acids such as lactic acid, acetatic acid and propionic acid that demineralize enamel and dentin. As the carious lesion progresses into dentin, activation of endogenous, bound matrix metalloproteinases and cysteine cathepsins will lead to the degradation of collagen fibrils and decrease in the mechanical properties of dentin [2,3]. Prevention and treatment of dental caries is a major challenge because as many as nine out of ten adults in Western countries suffer from dental caries [4]. In the United States alone, more than 100 million dollars is spent annually on dental service. Despite significant advances in preventive and restorative dentistry, replacement of tooth fillings constitutes a substantial share of this annual dental expenditure, due to limited durability of contemporary resin-based restorative materials, particularly when these materials are applied to damaged dentin in the absence of a superficial enamel layer [5–7].

Apart from caries, resin–dentin bonding is another major reason for dentin demineralization [8]. The formation of resin–dentin bonds is accomplished predominantly by micromechanical retention via resin penetration and entanglement of exposed collagen fibrils in the partially or completely demineralized dentin. This is achieved by etching dentin with acids or acidic resin monomers derived from self-etching primers/adhesives to expose the collagen fibrils [7]. To date, it is impossible for resin monomers to completely displace water within the extrafibrillar and particularly the intrafibrillar compartments of a demineralized collagen matrix, and infiltrate the collagen network completely [8–10]. Even if this may be achieved, the limited intermolecular space (1.26–1.33 nm) between collagen molecules renders it challenging to accommodate even small, extended resin monomer molecules such as triethyleneglycol dimethacrylate (≈2 nm long) [11]. This invariably results in the presence of mineral-depleted, resin-sparse, water-rich collagen fibrils along the bonded interface [7,9]. Under the combined challenges of enzymes, temperature and functional stresses, regions of incomplete resin infiltration within the dentin hybrid layer is susceptible to degradation, resulting in damage of interfacial integrity, reduction in bond strength and ultimately, the failure of resin–dentin bonds. Thus, remineralization of demineralized dentin has important consequences for control of dentinal caries as well as improvement of dentin bonding stability [8,10].

Different strategies have been employed for remineralizing demineralized dentin. For instance, fluoride, amorphous calcium phosphate (ACP)-releasing resins or resin-based adhesives containing bioactive glass have been used to improve the resistance of bonded restorations to secondary caries [12–15] However, most of these studies focused on remineralizing partially demineralized carious dentin, which was based on the epitaxial deposition of calcium and phosphate ions over existing apatite seed crystallites [16]. With these traditional ion-based strategies, remineralization does not occur in locations where seed crystallites are absent [17]. Thus, the classical ion-based crystallization concept may not be applicable for remineralizing completely demineralized dentin within hybrid layers created by etch-and-rinse adhesive systems or the superficial part of a caries-affected dentin lesion left behind after minimally invasive caries removal, due to the unavailability of seed crystallites in those regions for accomplishing homogeneous nucleation of apatite crystallites [18,19].

Biomimetic remineralization represents a different approach to this problem by attempting to backfill the demineralized dentin collagen with liquid-like ACP nanoprecursor particles that are stabilized by biomimetic analogs of noncollagenous proteins [20–22]. This is achieved by adopting the recently discovered, non-classical particle-based crystallization concept utilized by Nature in various biomineralization schemes, ranging from the mineralization of sea-shells (calcium carbonate), siliceous shells of diatoms and sponges (amorphous silica) to the deposition of calcium phosphate salts in fish scales and bone [23,24]. Intrafibrillar mineralization of fibrillar collagen not only significantly increases its mechanical properties [25–28], but also protects the collagen molecules from external challenges, such as temperature, endogenous enzymes, bacterial acids and other chemical factors. Using this biomimetic remineralization strategy, both hybrid layers created by etch-and-rinse adhesives [21,29,30] and moderately aggressive self-etch adhesives [18,31,32], as well as 250–300 μm thick completely demineralized dentin lesions can be remineralized [33,34]. This bottom-up remineralization strategy does not rely on seed crystallites, and may be considered as a potentially useful mechanism in extending the longevity of resin–dentin bonds [35] via restoring the dynamic mechanical properties of the denuded collagen within the hybrid layer to approximate those of mineralized dentin [36]. This paper reviews the changing concepts in calcium phosphate remineralization and the progress in clinical translation of the biomimetic dentin remineralization strategy.

2. Changing concepts of calcium phosphate biomineralization

Biomineralization is the process by which living organisms secrete inorganic minerals in the form of biominerals (e.g. magnetite, silica, oxalates, various crystalline forms of calcium carbonate and carbonated apatite) within cell cytoplasm, shells, teeth and bony skeletons [37,38]. This process exhibits a high level of spatial and hierarchical control as mineralization usually takes place in a confined reaction environment under ambient temperature and pressure conditions. Calcified human tissues consist of the collagen matrix and the hierarchically arranged carbonated apatite inorganic phase; deposition of the latter is regulated by non-collagenous proteins [39,40]. It is generally believed that non-collagenous proteins, along with specific MMPs and other important enzymes secreted by odontoblasts, play critical roles to orchestrate dentin mineralization. They possess carboxylic