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DENTIN BIOMODIFIERS USED IN DENTISTRY

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ABSTRACT

The vast majority of aesthetic dental restorations are performed using resin composites. Ensuring a durable bond between the tooth surface and the adhesive resin is crucial for the long-term success of composite restorations in clinical practice. While adhesive systems have made significant advancements, the bonded interface continues to be the least robust aspect of resin-based restorations. The primary reason for this is the degradation of exposed collagen at the base of the hybrid layer, which results in a decline in the resin-dentin bond. Researchers are currently exploring different dentin biomodifiers to mitigate the enzymatic breakdown of collagen and enhance their mechanical durability. Dentin biomodification utilizes matrix metalloproteinase inhibitors and collagen cross-linkers on acid-conditioned dentin. While the research is still in its early stages, dentin biomodification shows promise as a method to enhance the stability of the resin-dentin bond. This paper provides a concise overview of various dentin biomodifying agents, their mechanisms of action, and their impact on enhancing the durability of the resin-dentin bond.

KEYWORDS: Resin-dentin bond; Matrix metalloproteinase inhibitors; Collagen cross linkers; Bond durability.

INTRODUCTION

Dental caries is a common issue globally, and resin composites are commonly employed as filling materials.[1] Nevertheless, the longevity of resin-based restorations is suboptimal, with failure rates varying between 15% and 50%.[2] Moreover, resin-dentin bonds exhibit lesser durability compared to resin-enamel bonds due to the heterogeneous nature of dentin's structure and composition.[3] When resin-dentin bonding fails, it leads to issues such as microleakage, staining, recurrent caries, and postoperative sensitivity.[4] The interplay of these factors can further hasten the degradation of the bond. Despite considerable advancements in adhesive systems, the bonded interface remains the weakest aspect of resin-based restorations.[5] Enhancing the chemical and mechanical stability of collagen fibrils within the hybrid layer could be clinically significant for improving the durability of resin-dentin bonds. Consequently, this paper aims to explore factors contributing to the failure of resin-dentin bonds and to discuss various dentin biomodifying agents currently under research, aiming to optimize the longevity of resin-dentin bonds.

FACTORS LEADING TO RESIN- DENTIN BOND FAILURE

1. DIFFERENCE NOTED BETWEEN RESIN INFILTRATION AND DENTIN DEMINERALIZATION DEPTH: In etch and rinse systems, the discrepancy arises from the variation in the depth of penetration of the adhesive compared to the action of the acid etchant. This incomplete hybridization of the exposed collagen network results in collagen fibrils at the base of the hybrid layer remaining uninfused, making them more vulnerable to hydrolytic degradation. Resin monomers cannot fully replace both free and collagen-bound water within the inter and intrafibrillar compartments, which hinders the attainment of a complete and stable hybrid layer. Moreover, highly hydrated proteoglycan hydrogels within the interfibrillar spaces function as filters, capturing large molecule monomers like BisGMA while permitting the passage of small monomers like HEMA toward the hybrid layer's base.[6]

2. DEGRADATION OF THE ADHESIVE RESIN: Employing hydrophilic monomers HEMA in adhesive systems aims to enhance the infiltration of the naturally humid exposed collagen network. This leads to an immediate enhancement in bond strength, although the

long-term durability of this dentin-resin bond is compromised.[7] In the presence of water, a weak hybrid layer forms at the adhesive interface, characterized by hydrolysis and leaching of resin adhesives. Modern adhesives comprise both hydrophilic and hydrophobic components that, when in contact with water, undergo nano phase separation.[8]

3. DEGRADATION OF EXPOSED COLLAGEN: The demineralized dentin collagen matrix serves as a scaffold for resin infiltration during resin-dentin bonding, forming the hybrid layer. However, degradation of these collagen matrices by matrix metalloproteinases (MMPs) and cysteine cathepsins is considered a major factor in the failure of resin restorations. MMPs and cysteine cathepsins have the ability to attack type I collagen, which is the predominant organic component of dentin.[9] These enzymes can be activated by various factors such as proteinases, chemical agents, low pH, heat treatment, and mechanical stress.[10] Acid-etchants used in dentin bonding can uncover and activate matrix-bound MMPs, and incomplete resin infiltration can also contribute to their activation. As a result, the exposed dentin collagen loses its protective triple helical conformation, exposing cleavage sites that make it more susceptible to MMPs and cathepsins.[11]

DENTIN BIOMODIFICATION

This approach aims to achieve a more stable and durable adhesive interface. Dentin biomodification can be accomplished using synthetic compounds like carbodiimide, glutaraldehyde, chlorhexidine (CHX), tetracyclines, quaternary ammonium compounds, ascorbic acid, as well as natural products such as quercetin, baicalein, catechins, oligomeric proanthocyanidins, genipin, hesperidin, and other polyphenols.[12]

DENTIN BIOMODIFIERS

PROANTHOCYANIDIN: Proanthocyanidins (PAs) belong to a class of bioflavonoids found naturally in various plant sources like fruits, vegetables, nuts, seeds, flowers, and barks. These compounds are composed of flavan-3-ol oligomers with three rings: a triketide ring (ring A), a phenylpropanoid ring (ring B), and a pyran ring (ring C) formed through condensation.

PAs are renowned for their diverse physiological activities, including antioxidant, antimicrobial, and anti-inflammatory properties. They also exhibit enzyme inhibition activities against phospholipase A2, cyclooxygenase, and lipooxygenase.[13]

In dentistry, PA has gained attention as a natural collagen cross-linking agent. Numerous studies have demonstrated that PA acts as a stabilizer for dentin collagen matrix, enhancing its mechanical properties and resistance to biodegradation.[14,15]

CHLORHEXIDINE: Chlorhexidine (CHX), a biguanide antimicrobial agent, is widely used in dentistry due to its effectiveness against microbes and its ability to remain active over time.[16] Even at a low concentration CHX is recognized as the most widely accepted non-specific matrix metalloproteinase (MMP) inhibitor. The mechanism of CHX in inhibiting MMPs likely involves a cationic-anionic reaction with the glutamic acid residue of the cysteine domain, potentially altering the structure of MMP molecules and preventing their binding to substrates.[17] CHX not only inhibits MMPs but also forms electrostatic bonds with demineralized dentin.

EDTA: EDTA functions as a chelating agent by reacting with calcium ions present in dentin hydroxyapatite, forming soluble calcium salts. Because EDTA is proficient at chelating both zinc (Zn^{2+}) and calcium (Ca^{2+}) ions, it may inhibit matrix metalloproteinase (MMP) activity.[18] Treating dentin beams with a 17% EDTA solution has shown to significantly reduce endogenous MMP activity in fully demineralized dentin beams because EDTA chelates calcium and zinc ions from the enzyme, impairing their optimal function.

GLUTARALDEHYDE: Glutaraldehyde (GA) is primarily used as a fixative that cross-links collagenous biomaterials. It contains two aldehyde groups capable of reacting with the amino groups of lysyl or hydrolysyl polypeptide residues in collagen, thereby forming reducible Schiff base crosslinks. GA can effectively enhance the resistance of uncross-linked or mildly cross-linked collagen matrices to degradation by collagenases.[19] However, it is found to be approximately 120 times more toxic than proanthocyanidins.[20]

GENIPIN: Genipin is derived from geniposide found in Gardenia jasminoides ellis fruits. This compound has a unique ability to form crosslinks with collagen molecules, particularly with primary amine groups. When applied to bovine dentin, genipin has demonstrated a notable increase in collagen fibril resistance against enzymatic breakdown, with the effect varying based on concentration and duration of exposure.[21]

HESPEREDIN: Hesperidin (HPN) is a flavonoid glycoside found in citrus fruits. Its medicinal properties are quite diverse, with benefits ranging from anti-inflammatory and analgesic effects to antimicrobial and antioxidant properties. Additionally, HPN has shown potential in inhibiting carcinogenesis, preventing bone loss, and inhibiting the proteolytic activities of matrix metalloproteinases (MMPs), which are enzymes involved in collagen degradation.[22]

CHITOSAN: Chitosan is derived from the deacetylation of chitin, which is commonly found in the exoskeleton of crustaceans.

One notable application of chitosan is its ability to enhance the resistance of dentin collagen against degradation by collagenase. When dentin collagen is coated with chitosan nanoparticles, it shows a significant increase in resistance to degradation, which is beneficial for maintaining dental tissue integrity. Additionally, chitosan has been found to increase the microhardness of the root dentin layer, indicating its potential for strengthening dental structures.[23]

CHEMICALLY MODIFIED TETRACYCLINES (DOXYCYCLINE AND MINOCYCLINE): Indeed, broad-spectrum MMP inhibitors like modified tetracyclines exhibit their inhibitory effects across multiple stages involved in MMP activity. These inhibitors act by interfering with MMP transcription, protein synthesis, and enzyme activation, particularly through binding within the MMP active site.

One key mechanism of action is their ability to chelate essential ions like Ca+2 and Zn+2, which are vital for maintaining MMP structure and functional active sites. By binding to these active sites, modified tetracyclines alter the conformation of the proenzyme (pro-MMP), preventing its transformation into an active enzyme and thus blocking its catalytic activity within the extracellular matrix.[24]

BAICALEIN: Baicalein, a major flavonoid found in Scutellaria baicalensis, acts as an MMP inhibitor and cross-linker. Its ability to inhibit MMPs and facilitate cross-linking makes it valuable for stabilizing collagen fibrils and maintaining the integrity of the hybrid layer in dentin bonding processes. Baicalein achieves its cross-linking effects through hydrogen bonds formed between its hydroxyl groups and amide carbonyls in proteins. This property allows it to act as a potential cross-linker, not only for proteins but also for proteases.[25]

Bacalein competes with the enzyme's active center through metal chelation, particularly by grabbing metal ions like Zn2+ that are essential for MMP activity. It may alter the three-dimensional structure or molecular mobility of MMPs through cross-linking, leading to a loss of their collagen enzymolysis ability and it can cross-link with dentin collagen fibers via hydrogen bonds, which may change or cover MMP recognition sites in collagen, interfering with enzymatic coordination and protecting non-coated collagen from degradation.

QUERCITIN: Quercetin is a flavonol compound commonly found in various foods like onions, apples, tea, and red wine. Its cross-linking properties have been studied extensively, showing potential benefits for enhancing the mechanical properties and thermal denaturation temperature of the extracellular matrix. Apart from its structural benefits, quercetin also offers a range of health advantages, including anti-inflammatory, antioxidant, and potential cancer-preventing properties. In specific contexts, quercetin has demonstrated its ability to inhibit the activity of MMP-2 and MMP-9, which are matrix metalloproteinases involved in various cellular processes.[26]

One notable mechanism of action is quercetin's ability to cross-link with collagen, leading to decreased formation of water canals within collagen structures. This cross-linking property helps resist collagenase attacks, thereby strengthening collagen stability.

CASHEW NUTSHELL LIQUID: Cardol and cardanol, which make up more than 95% of technical cashew nutshell liquid (CNSL), have garnered attention for their potential in dentin biomodification. The long 15-carbon alkyl side chain in these compounds allows for enhanced hydrophobic interactions with dentin collagen fibrils, which could contribute to modifying the dentin structure.[27] Despite their hydrophobic nature, cardol and cardanol are non-cytotoxic at low concentrations and exhibit antioxidant properties. Moreover, they have been found to inhibit matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), enzymes involved in tissue remodeling and degradation.

Overall, cardol and cardanol in CNSL offer a promising avenue for dentin biomodification, combining non-cytotoxicity, antioxidant effects, MMP inhibition, and effective penetration into dentin collagen for improved bond strength and structural modification.

CURCUMIN: Curcumin, derived from Curcuma longa, is a well-known and non-toxic polyphenolic compound. It's typically extracted from the plant's rhizome and contains three major curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin.

In terms of its interaction with matrix metalloproteinases (MMPs), curcumin's mechanism can be attributed to its ability to chelate catalytic Zn+2 ions, which are crucial for MMP activity. This chelation occurs via the β-diketone zinc-binding site present in curcumin, similar to how tetracycline-based MMP inhibitors work.

BROMELAIN ENZYME: Bromelain is an enzyme that breaks down proteins and is classified as a protease. It is extracted from pineapple fruit or stems for commercial use. Proteases like bromelain catalyze the hydrolysis of proteins into amino acids. Bromelain enzyme has been found to reduce nano leakage following collagen removal, possibly due to collagen depletion on acid-etched dentin surfaces, leading to increased permeability of the dentin substrate caused by enlarged dentinal tubules near the outer dentin surface. This enlargement aids in the spread and diffusion of adhesive monomers through the dentin. Additionally, enhancing the surface energy of dentin occurs because hydroxyapatite, with high surface energy, replaces collagen with a lower energy surface, thus promoting improved diffusion of adhesive monomers through the dentin.[28]

BENZALKONIUM CHLORIDE (BAC): Benzalkonium chloride is a blend of alkylbenzyl-dimethyl ammonium chlorides with varying lengths of alkyl chains. It is a cationic surface-acting agent that contains a quaternary ammonium group. Like biguanides, BACs only adhere to dentin collagen through electrostatic interactions, which means they might leach from the hybrid layer, losing their self-degrading benefits. Concentrations of BAC ranging from 0.5-1.0wt% or higher can inhibit rhMMP-2, 8, and 9 by up to 100%.[29] Similarly, these concentrations of BAC can inhibit matrix-bound MMPs by 55% to 76% over a 30-day period. Consequently, BAC can be classified among quaternary ammonium compounds.[30]

CONCLUSION

As composite restorations are widely used for managing caries, it's crucial to grasp the challenges related to the durability of resin-dentin bonds. While several studies have explored the impact of MMP inhibitors and collagen cross-linkers in extending the lifespan of resin-dentin bonding, further research is needed to create new bonding systems. These systems should offer robust MMP-inhibitory properties and collagen crosslinking functionality to stabilize the hybrid layer. By doing so, they can enhance the durability of adhesive composite restorations and address ongoing concerns in this area.

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