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Cross Linking Agents in Adhesive Dentistry-A Systematic Review

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Abstract

Dental adhesives are one of the most intriguing biomaterials in health sciences. Adhesion to dentin depends on the formation of the hybrid layer which is the weakest link in the resin– dentin interface because collagen fibrils that are not completely infiltrated by resin are vulnerable to enzymatic degradation over time. Several strategies therefore have been discovered to further improve bonding and to counteract the main bond-degradation pathways. Dentin biomodification is a biomimetic technique of improving and reinforcing the dentin by modifying the biochemistry and biomechanical qualities locally utilizing bioactive agents. Understanding the hierarchical structure of dentin and the targeted effect of the bioactive compounds will lead to their use in dentin- biomaterials interface as well as caries management. This review provides an overview of

essential dentin matrix components, biomodification strategy targeting effects, the chemistry of renewable natural sources and current research on their potential clinical applications.

Keywords: dentin, collagen cross-linking, proanthocyanidin, carbodiimide, riboflavin, polyphenols.

Introduction

Dentin adhesion is like in-situ tissue engineering, in which collagen fibrils exposed by acid etching act as a scaffold for micro-mechanical interlocking of monomers leading to formation of hybrid layer. To achieve a stable hybrid layer, the resin infiltration into the exposed collagen fibres should be as complete as possible. However, with etch-and-rinse adhesives, inadequate penetration of the exposed collagen matrix is frequent.[1].

The moisture of demineralized dentin also hinders the infiltration of hydrophobic monomers [2]. This variation between the depth of demineralised collagen layer and resin infiltration leads to denuded exposed collagen fibrils at the bottom of hybrid layer, lacking the protection of polymerized resin. This is a vulnerable section where stress tends to concentrate and most failures occur [3,4]. While bonding to enamel has shown to be reliable over-time, bonding to dentin is a great challenge [5,6]. Dentin represents the bulk of the tooth structure, and a reliable long-term bond is essential for the success of adhesive restorations. Even with the challenges associated with degradation of the dentin-adhesive interface over time, continuous research has been done to improve the mechanical properties of this adhesive interface [7].

Recently, dentin biomodification has been employed to achieve a more durable and stable adhesive interface [8]. It involves the use of many natural and synthetic agents, acting as a collagen cross-linker and MMP inhibitor to bio-modify and enhance the mechanical properties of the dentin [9].

Review of literature

Collagen cross-linking compounds have been proposed as adjuvants in restorative operations to strengthen the structural stability of dentin collagen by the addition of intermolecular and intramolecular connections, as well as the durability of resin-dentin attachment [10]. Table 1 summarizes currently investigated cross- linking agents in adhesive dentistry. With a focus on naturally occurring polyphenols because of their superior bioactivity, biocompatibility, and applicability when compared to other well- known agents [8].

TYPES		DENTIN MATRIX INTERACTION	
		MECHANICAL PROPERTIES	ENZYMATIC DEGRADATION
Physical methods			
	Riboflavin/UVA Radiation	N/N	+
Chemical agents			
Synthetic	Gluteraldehyde	+++	+
	Carbodiimide	++	+
	Chlorhexidine	++	+
Natural	Genipin	+	+
	Polyphenols		
	Proanthocyanidines	++++	+
	Other polyphenols	-/+++	+

N/N, not known/not reported; +, positive; -, no effect

Physical methods

Synonymous to photo-oxidative method; ultraviolet radiation is used in most of the synthetic bio modifiers [11-12]. This requires the presence of singlet oxygen; and one of the most potent producer of oxygen radicals is riboflavin (vitamin B2) [13], used in conjunction with ultraviolet A- generates oxygen free radicals by breaking down the intrinsic bonds of collagen. Proline or lysine in collagen is attacked by the hydroxyl functional clusters in riboflavin promoting formation of new cross-links. This increases resistance to collagen degradation and improves the tensile strength [10,14].

Riboflavin has ability to produce free radicals when photo-activated with spectral range from UV to visible light spectrum with three maximum absorption peaks at 270, 366 and 445 nm. These free radicals, or so-called reactive oxygen species such as O2 and $O2^{-}$, are released when riboflavin is photo-activated and light is absorbed, forming covalent crosslinks between adjacent collagen molecules. Although the spectral absorption of riboflavin is much higher at 270 nm, due to safety precautions related to ultraviolet B (UVB), it is not recommended for clinical applications. Riboflavin has narrow spectral absorption peaks at 366 nm Ultraviolet A (UVA) and 445 nm wavelengths (visible blue light).

UVA rays effectively activate riboflavin, visible blue light shows a promising substitute for UVA as it is clinically more applicable and acceptable, and still manages to increase the resistance to biodegradation, enhance the mechanical properties of dentin collagen and improve and maintain the bond strength and interface integrity after short-term water storage [15].

Chemical agents

Chemical cross-linking agents can be synthetic or natural resources.

Synthetic resources

Gluteraldehyde (GA): Increased tensile strength and elasticity and the ability to reduce degradation by the action of glutaraldehyde on the free amino groups of collagen such as lysine and hydroxylysine [16,17]. Cytotoxicity limits the clinical applicability of this material [18].

Carbodiimide hydrochloride (EDC): Used as an alternative to glutaraldehyde as it is less cytotoxic [19, 20]. Also called as a zero-length agent as it has the ability to cross-link peptides without introducing additional linkage groups. The activation of carboxylic acid groups in glutamic and aspartic acids to create an O-acylisourea intermediate mediates the cross- linking action. The latter forms an amide cross- link with the -amino groups of lysine or hydroxylysine, leaving urea as a terminal by-product. N-hydroxysuccinimide (NHS) is effective in boosting the amount of induced collagen cross-linking and limiting the hydrolysis of activated carboxyl groups when added to an EDC-containing solution [21,22]. Despite this, cross-linking potential is limited [23]. Chlorhexidine: An antimicrobial agent broadly used in dentistry is also used to inhibit MMPs 2, 8 and 9 without inducing cytotoxic effects [24]. Presents with collagen cross-linking ability, preservation of bond strength and reduced interface degradation, expressed by reduction of nanofiltration even at low concentrations of 0.2% was seen. The inhibition occurs due to the proteases which chelate calcium ions [25,26]. But it has low substantivity when applied to dentin [27].

Natural resources

The most attractive characteristics being lower cytotoxicity and renewability over the synthetic resources, leading to intense studies in the past decade [28]. Sources like Genipin (Gardenia jasminoides) has slow cross-linking ability and have limited applications [29]. A nitrogenous iridoid derivative that undergoes dehydration to produce an aromatic monomer when reaction between free amino acids (lysine, hydroxylyisine, or arginine) takes place to form inter- and intra- molecular cross-links [30-32]. Polyphenols from plants have been linked to a wide range of bioactivities. Their biological functions are the foundation for their major roles in plant-based dietary supplements and nutritionals, and novel applications are being explored by contemporary research. The proanthocyanidins belonging to condensed tannins are highly hydroxylated structures forming an insoluble complex with proteins and carbohydrates are particularly interesting for dental use

[33]. They are anti-microbial, increases collagen synthesis and are also anti-tumorigenics [34]. When proanthocyanidins and collagen interact, complexes arise that are thought to be stabilised primarily by hydrogen bonding between the protein amide carbonyl and the phenolic hydroxyl [35], as well as covalent and hydrophobic interactions. The relatively high stability of proanthocyanidins-protein complexes suggests structural specificity [36], which promotes hydrogen binding while simultaneously generating hydrophobic pockets [28]. Such a microenvironment reduces the dielectric constant and increases the stability of such H bonds. Its non-specific inhibition of protease activity and its interaction with proteoglycan have expanded its dental use. As with other naturally occurring drugs, the preparation of a PAC source of raw material is essential to determine its interaction with tissues [4].

Proanthocyanidines: Have been under study for 15 years in dentistry and are derived from plants [28]. Structurally they consist of cathecin and epicathecin, interflavonoid bonds and several chain lengths, known as degree of polymerization [37]. Some sources of proanthocyanidins are already tested such as tea plant leaves (Camellia sinensis), cocoa seed (Theobroma cacao), cinnamon bark stem (Cinnamon Verum), açaí fruit (Euterpe precatory) and bark of pine tree (Pinus massoniana). The one that showed better results in dentin was the grape seed (Vitisvinifera) [3,38]. Application of proanthocyanidin to human dentin improves biomechanics and biostability that mimics crosslinking of other levels of collagen by non-enzymatic interactions [39]. In addition, the resistance to biodegradation [40] of as well as the tensile strength properties [41] and the elastic modulus [42] are improved. The ability to bind to proline-rich proteins acted favorably on collagen fibers and immediate adhesion and stabilization in demineralized dentin [38]. Liu et al. [43] proved that the activity of both collagen degradation and gelatin degradation of demineralized dentin was shown to be inhibited by PAC-modulated dentin biomodification. Cardol and cardanol: Cashew nut derivatives (LCC, Anacardiumoccidentale), are already tested as dentin desensitizers [44] and to evaluate mechanical properties of dentin [45]. These are phenols capable of cross-linking through hydrogen bonds which are responsible for hydrophobic characteristics [46].

Aroeira extract (Myracrodruon urundeuva), is an anti-inflammatory agent and antimicrobial. When tested in dentin showed improved mechanical properties of dentin and degradation [45]. Epigallocatechin 3-gallate (EGCG): The major polyphenol in green tea (Camellia sinensis) and inhibitor of MMP (2 and 9). Has potent antibacterial activity against Gram-positive and Gram-negative bacteria with cross-linking ability [47].

Curcumin: A naturally occurring pigment that is part of an active component of dentin-tested saffron, producing reduced MMP activity in pre- treated samples with biomodification agents [48], it also decreases gelatinolytic activity and reduces release of MMP-2, MMP-8 and MMP-9 [48]. Curcumin also demonstrated complete efficacy against cathepsin K-mediated collagen degradation and generated lesser dry mass loss than other biomodification agents [49].

Chitosan: Chitosan is a cationic polymer made by deacetylating chitin, a polysaccharide found in crab exoskeletons, using an alkalinization method at high temperatures. Chitosan as a biological agent has been the subject of a recent investigation in experimental restorative dentistry. Chitosan significantly increased the resistance of collagenase to degradation after ocolagene is coated with nanoparticles of chitosan (CSnp). It also increased the microhardness of root dentin [50], to add to,

chitosan modified methacrylate improves durability of etch and rinse adhesive restorations [51]. Furthermore, using chitosan/riboflavin to alter collagen dentine in specific proportions stabilises the collagen fibrillar network, allowing better resin infiltration and hybrid layer formation [52]. Chitosan has been used at surgical sites and non-surgical periodontal therapy as a gel made from various granulations and concentrations of the powder of this biomaterial. Chitosan may be incorporated into various restorative materials such as glass ionomer in concentrations of 5 to 50% and in adhesive systems in concentrations of 0.12% to 1%. Collagen cross linkers can be used as pre-treatment agents adding an additional step in etch and rinse adhesives. Collagen cross linkers should definitely be included in etching agents because they won't add any extra steps to the bonding process. The most feasible method will be to incorporate into an adhesive, which is yet to be improved and modified to maintain the quality of adhesive.

Conclusion

Although early resin-dentin bonding agents are excellent, adhesive interface deterioration is aprevalent concern that affects the restoration's lifespan. Based on current literature, improvements in the adhesive systems contributes to making the bond of restorations bond to dentin stronger and more durable. Because of their biocompatibility, high dentin bioactivity, and availability as renewable materials, proanthocyanidins appear to be most promising. Several new innovative products are expected in the near future comprising of cross- linking agents to modify resin-bond adhesive systems.

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