Med Pregl 2024; LXXVII (7-8): 241-247. Novi Sad: juli-avgust.

REVIEW ARTICLES
PREGLEDNI ČLANCI

CONTEMPORARY METHODS OF THE IMPROVEMENT OF RESIN-DENTIN BONDS – A LITERATURE REVIEW

SAVREMENE METODE ZA UNAPREĐIVANJE VEZE IZMEĐU ADHEZIVNIH SMOLA I DENTINA – PREGLED LITERATURE

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Review article
UDK 616.314-74:615.46
https://doi.org/10.2298/MPNS2408241B

Abstract

Introduction. Despite significant advancements in materials for permanent restorations, there is still no material that fully replicates the physical, chemical, and biological properties of dental tissues. Contemporary research in adhesive dentistry focuses on achieving a reliable and durable bond between restorative materials and dental substrates. This paper aims to present recent innovations in dental technology focused on improving the challenging bond between restorative materials and dentin. Currently, several key strategies address this issue, including the application of collagen cross-linkers, antioxidants, inhibitors of endogenous proteinases, reinforcement with inorganic fillers and remineralization agents, modifications in bonding techniques, and substrate treatment using lasers. **Conclusion.** Current knowledge and experimental findings suggest that modern methods of modifying the dentin substrate can achieve a satisfactory initial adhesive bond. However, the degradation of the interfacial contact surface remains a significant challenge, compromising the long-term durability of restorations.

Key words: Dentin-Bonding Agents; Adhesives; Dentin; Collagen; Matrix Metalloproteinases

Sažetak

Uvod. Uprkos raznovrsnosti i unapređenju materijala za definitivne ispune, još uvek ne postoji materijal koji u potpunosti odgovara fizičkim, hemijskim i biološkim osobinama zubnih tkiva. Savremena istraživanja u oblasti adhezivne stomatologije usmerena su na postizanje adekvatne i predvidljive veze između restaurativnih materijala i zubnog supstrata. Cilj ovog rada je da predstavi novija dostignuća dentalne tehnologije kojima bi se unapredila, još uvek, kontroverzna veza restaurativnih materijala sa dentinom. Trenutno postoji nekoliko glavnih strategija za rešavanje ovog problema koji uključuju: umreživače kolagena, antioksidante, inhibitore endogenih proteinaza, ojačavanje matriksa smole neorganskim puniocima i/ili agensima za remineralizaciju, modifikaciju tehnike adhezivnog vezivanja i tretiranje supstrata laserom pre adhezivnog vezivanja. **Zaključak.** Na osnovu trenutnih znanja i eksperimentalnih istraživanja može se zaključiti da se primenom savremenih metoda modifikacije dentinskog supstrata postiže adekvatna inicijalna adhezivna veza. Međutim, degradacija međufazne kontaktne površine još uvek predstavlja čest problem, koji kompromituje dugovečnost restauracija.

Ključne reči: dentinski adhezivni agensi; adhezivi; dentin; kolagen; matriks metaloproteinaze

Introduction

The primary objective and greatest challenge in adhesive dentistry is achieving a predictable and durable bond between dental substrates and restorative materials. A reliable bond ensures strong retention, minimal microleakage, and restoration stability [1, 2]. The strength and effectiveness of this bond are influenced by several factors, including the physical and chemical properties of dental tissues and restorative materials. Additionally, external factors such as the oral environment – humidity, mastication, diet, temperature fluctuations, and variations in saliva pH – exert significant effects and should not be overlooked.

Micro-mechanical bonding to dentin relies on forming a resin-reinforced dentin layer known as the "hybrid layer". This layer is created when adhesive resin penetrates the extracellular dentinal matrix, primarily composed of collagen fibrils. Consequently, the stability of the collagen matrix is critical for maintaining the integrity and stability of the hybrid layer, which improves the mechanical properties and longevity of the bond [3–5]. However, numerous studies have revealed that mechanical and ultrastructural changes within the hybrid layer occur over time, indicating

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Abbreviations

MMPs – matrix metalloproteinases
PA – proanthocyanidins
DMA – N-(3,4-dihydroxyphenethyl) methacrylamide
CHX – chlorhexidine
BAC – benzalkonium chloride
EDTA – ethylenediaminetetraacetic acid
DMSO – dimethyl sulfoxide
Er:YAG – Erbium-doped Yttrium Aluminium Garnet

its limited durability. Factors contributing to these changes include deficient infiltration of adhesive resin into demineralized dentin and the elution, or separation of residual monomers from the polymerized adhesive resin. Exposed collagen fibers within the hybrid layer that remain unprotected by resin are susceptible to degradation over time.

Matrix metalloproteinases (MMPs) are zinc and calcium-dependent endopeptidases whose activity can be observed in many biological and pathological processes related to the degradation of the extracellular matrix. Various MMPs, such as stromelysin-1 (MMP-3), collagenase (MMP-8), and gelatinases A and B (MMP-2 and MMP-9), have been identified in dentin substrates [6]. More recently, matrilysin-1 (MMP-7) has been also been detected [7]. While MMPs contribute to dentin maturation, they become inactive after the mineralization of the collagen matrix [6]. Endogenous MMPs are inactive in dentin; however, they are reactivated in certain conditions such as reduced pH in the environment caused by caries or etching. Proteases gradually degrade collagen fibers, leading to the deterioration of the bonding surface and a reduction in bond strength, which can range from 36% to 70% within 12 to 14 months [8, 9].

In recent years, numerous studies have been published about the deterioration of bond strength in adhesively bonded restorations. According to research, advances in dental technology have provided several approaches to address this issue, which are explored in this paper [6]. The objective of this study is to review and highlight recent developments in dental technology aimed at improving the still-challenging adhesive bond between restorative materials and dentin.

I Collagen Cross-Linkers

In biological sciences, the term "cross-linking" refers to the formation of chemical bridges during chemical reactions between proteins or other molecules, resulting in altered physical properties of biological molecules [10].

Collagen fibers are composed of myofibrils interconnected by endogenous covalent cross-links. Cross-links formed using external cross-linkers are notably stable over extended periods, as the formation of covalent bonds is irreversible. Demineralization of tissue leads to a significant reduction in collagen matrix stiffness, decreasing from 18,000 MPa to 1-3 MPa. This low modulus of elasticity allows free movement of collagen fibers, including lateral and rotational shifts, which expose active binding sites for MMPs [2]. Additionally, cross-linking agents have been shown to inhibit MMP actively by reducing molecular mobility, inducing conformational changes in collagen structure, or converting negatively charged carboxyl groups into positively charged amides [2]. Recent studies suggest that pretreating dentin or enriching adhesive systems with natural or synthetic collagen cross-linking agents improves the mechanical properties of collagen and enhances the adhesive bond [2].

Several natural substances exhibit collagen cross-linking properties, including proanthocyanidins (PA), polyphenols from green tea extract (EGCG) [11], naringin [2], chitosan [12, 13], riboflavin [14], genipin, bromelain enzyme [6], curcumin [15, 16], black tea flavonoids [17], eucalyptus lignin, cardanol from Indian cashew nutshells [18], and urushiol [19]. Among these, chitosan stands out for its unique properties and versatility. Chitosan, a semi-synthetic molecule derived from an amino-polysaccharide and created through the partial acetylation of chitin [12, 13], is valued for its biocompatibility, biodegradability, and low toxicity. In dentistry, chitosan has applications in caries prevention, mechanical integrity enhancement, antimicrobial treatments, and tissue regeneration. Research indicates that chitosan improves bond strength and longevity in dental restorations, particularly in etch-and-rinse or self-etch adhesive systems. However, its effectiveness depends on its concentration and specific application. While lower concentrations (0.12% to 0.25%) enhance bonding strength, higher concentrations (0.5% and 1%) may reduce bonding efficacy.

Among synthetic cross-linkers, commonly used agents include glutaraldehyde, carbodiimides, and DMA monomers etc. [6, 9, 20–24]. One notable compound is N-(3,4-dihydroxyphenethyl) methacrylamide (DMA), inspired by adhesive proteins of mussels. These shellfish found worldwide exhibit unique wet adhesion properties that enable them withstand harsh marine environments, such as turbulent currents and protease degradation. This behavior parallels the demands on the resin-dentin interface in the oral cavity, which must endure daily mechanical stresses, temperature fluctuations, pH variations, and proteolytic attacks. Researchers have sought to translate the adhesion properties of mussels into dentin bonding treatments, yielding promising in vitro results. One such compound, N-(3,4-dihydroxyphenethyl) DMA, is incorporated into dental adhesives due

to its ability to polymerize with adhesive monomers and cross-link with dentin collagen via non-covalent bonds. This significantly enhances the durability and mechanical properties of the resin-dentin interface. Furthermore, DMA monomers exhibit hydrolytic stability and inhibit MMPs, thereby protecting the integrity of the hybrid layer. The incorporation of DMA monomers has demonstrated potential in improving bond strength, reducing nanoleakage, and extending the longevity of dental restorations, making them a valuable addition to modern adhesive systems. However, challenges remain, such as the limited shelf life of these monomers due to the oxidation of catechol groups, necessitating further research to optimize their application. Notably, one-minute pretreatment with a DMA-EtOH primer has been shown to enhance resin-dentin interface integrity, inhibit endogenous MMP activity, and prolong resin-dentin bond durability [20].

II Antioxidants

The polymerization process of resin-based materials can be disrupted by oxidizing agents, which are generated in dental substrates during clinical procedures such sodium hypochlorite and tooth whitening with hydrogen peroxide-based products [6]. Contemporary research suggests effective strategies to overcome this issue, including the use of proanthocyanidins (PA), noni fruit juice (Morinda citrifolia), vitamins C [15] and E, as well as quercetin. When applied to dentin treated with sodium hypochlorite before the adhesive system is used – or when incorporated into the primer or adhesive resin - these oxidants have demonstrated the ability to neutralize the oxidative effects of sodium hypochlorite. By restoring the redox potential of oxidized dentin, they create conditions conductive to effective polymerization [6].

III Inhibitors of Endogenous Proteinases

The most commonly used inhibitors of MMPs include:

1. Chlorhexidine

Chlorhexidine (CHX) is the most widely used MMP inhibitor. In addition to its antimicrobial properties, CHX inhibits MMPs through a chelating mechanism. It remains bound in dentin for at least 12 weeks or longer, especially in demineralized dentin. A study by Breschi et al. [23] demonstrated the presence of CHX ions in the hybrid layer even after 10 years of aging in artificial saliva, originating from the primer applied before adhesive bonding. This prolonged binding preserved MMP inhibition and provided ongoing protection of the hybrid layer. However, sodium chloride can displace CHX from both mineralized and demineralized dentin, indicating that CHX's binding mechanism is purely electrostatic [6]. CHX can be applied after acid etching or incorporated into any component of the adhesive system. Low concentrations (0.5-5%) are effective, while concentrations below 0.1% have been found to be ineffective [6]. The most common method of CHX application is in the form of a primer due to its widespread availability in dental offices and its rapid action, taking effect within 30 seconds [23].

2. Tetracyclines

Minocycline has been shown to enhance the strength and stability of the dentin-adhesive bond when applied after acid etching. A 2% minocycline solution applied post-etching effectively prevents the breakdown of the interfacial contact surface for more than two years [25]. As a chemically modified tetracycline (CMT), minocycline retains its ability to chelate calcium (Ca) and zinc (Zn) ions, which underlies its mechanism for inhibiting endogenous proteases. Similarly, doxycycline was demonstrated effectiveness [6]. However, its application involves a more complex technological process. Specifically, incorporating doxycycline into adhesive systems can result in phase separation, resulting in the absence of the desired effect of doxycycline [6, 26]. Care must be taken when using tetracyclines, as they may cause dark discoloration of dental tissues due to photodegradation process [23].

3. Quaternary ammonium compounds

Quaternary ammonium compounds, such as benzalkonium chloride (BAC), are positively charged at physiological pH, enabling them to inhibit proteases through a cationic mechanism similar to CHX. BAC binds strongly to demineralized dentin, providing an immediate inhibitory effect and maintaining the strength of the adhesive bond over time [23]. Commercially, BAC is available as a 1% antimicrobial conditioning agent incorporated into phosphoric acid etchant. In this form, it exhibits antiproteolytic properties but does not enhance the initial adhesive bond strength. Additionally, the rinsing step in total-etch protocols reduces the BAC concentration in the hybrid layer, limiting its inhibitory potential. Incorporating BAC into the primer or adhesive resin could improve its efficacy without extending clinical procedures [9, 27].

4. Ethylenediaminetetraacetic acid

Due to its chelating properties, ethylenediaminetetraacetic acid (EDTA) inhibits MMP activity by binding zinc and calcium ions when applied for 1 to 5 minutes. Additionally, EDTA enhances collagen infiltration by adhesive resin, likely due to the re-

moval of the smear layer, which facilitates improved monomer interaction. Studies have shown that adhesive bonds formed on dentin treated with EDTA are stronger compared to those treated with phosphoric acid. However, EDTA is easily washed away during rinsing, which may diminish its inhibitory effect [6].

5. α-tomatine

Tomatine is a glycoalkaloid found in all parts of the tomato plant, consisting of two glycoalkaloids – alpha-tomatine and dehydrotomatine [28]. Recent studies have revealed that alpha-tomatine can inhibit MMP-2 and MMP-9 activity in certain cancer cells, exhibiting anti-metastatic properties. In a study by Ucuncu et al. [29], alpha-tomatine and chlorhexidine were shown to exhibit differing inhibitory effects on various MMPs.In vitro experiments demonstrated that alpha-tomatine achieved higher bond strength than chlorhexidine and control groups across all subgroups, irrespective of dentin type [29].

IV Strengthening the resin matrix with inorganic fillers and/or remineralization agents

Given the hybrid layer's susceptibility to both enzymatic and chemical degradation of adhesive components, reinforcing the resin matrix is a promising approach to enhancing hybrid layer resistance. Functionalized nanoparticles of titanium dioxide, copper, silver, and zinc oxide, modified with carboxylic acid, have been utilized to strengthen the organic resin matrix [6]. Copper nanoparticles, in particular, serve as MMP inhibitors and exhibit cross-linking properties. Studies have demonstrated that adding copper nanoparticles at concentrations of 0.1% and 0.2% to total-etch adhesive systems significantly improves adhesive bonding to both healthy and caries-affected dentin [30]. Similarly, zinc (Zn) plays a dual role by promoting dentin remineralization and inhibiting demineralization. Zinc further contributes to bond durability through competitive enzyme inhibition, while also offering anti-inflammatory and antibacterial effects [31]. However, adhesive resins containing nanoparticles are prone to agglomeration and uneven filler dispersion due to their low viscosity, which can compromise the adhesive's strength and stability. Carbon nanotubes, composed of a hexagonal network of carbon atoms rolled into cylindrical nanostructures, present a promising solution. These structures are strong and rigid, with notable thermal and electrical properties. Recent findings suggest that carbon nanotubes can reinforce both the adhesive resin and the adhesive bond. Additionally, their ability to encapsulate various compounds provides a novel strategy for preventing adhesive bond degradation [6].

Biomimetic remineralization

A novel approach to preserving the hybrid layer involves biomimetic remineralization, a process that mimics natural tooth remineralization. This method aims to fill unoccupied spaces in the resin matrix with hydroxyapatite, facilitating the remineralization of collagen fibers and the fossilization of MMPs [22]. For this purpose, bioactive silicates and phosphoprotein analogs are employed, which can form apatite crystals within collagen fibers [6]. It is crucial, however, for remineralization agents to include MMP inhibitors. This is because the remineralization process requires time, during which the demineralized collagen fibrils must be protected from enzymatic degradation [22].

V Modification of the adhesive bonding technique

Strategies to improve the adhesive bond focus on eliminating unbound water or residual monomers from the hybrid layer.

1. Application of an additional layer of adhesive resin

One widely discussed approach involves applying a hydrophobic resin layer after completing the adhesive bonding protocol. This additional resin layer interacts with unbound surface monomers, reducing their presence on the interfacial contact surface. The results in a denser hybrid layer that offers greater resistance to tensile forces and degradation [32]. Oliveira et al. [33] demonstrated that applying a double resin layer using a self-etch adhesive systems lead to the formation of longer resin tags in both healthy and demineralized dentin [6].

2. Ethanol wet bonding

In clinical practice, ethanol-based adhesive systems are typically applied to water-saturated dentin following acid etching. However, this process is prone to microscopic phase changes within the adhesive [9]. To mitigate this risk, ethanol wet bonding has been proposed, substituting ethanol for water as the rinsing medium to eliminate residual water from the hybrid layer. This technique inhibits proteolytic enzymes through a dual mechanism: infiltration of voids between collagen fibers with adhesive resin, and absence of unbound water [9, 22, 34].

3. Dry bonding

Dry bonding eliminates residual water from the hybrid layer by utilizing 2-step self-etch adhesive systems. These systems employ a primer designed to gently etch dentin and infiltrate it with acidic monomers, followed by the application of an adhesive resin free of solvents. The primers contain a high concentration of acidic monomers with minimal water, sufficient to ion-

ize the monomers and dissolve the mineral phase of dentin. After self-etching for 10 seconds, the dentin surface is dried, and the adhesive resin is applied prior to light polymerization. The resulting hybrid layer contains a larger portion of the smear layer, including "smear plugs" that prevent the outflow of dentinal fluid during the adhesive bonding process [9, 22].

4. Application of dimethyl sulfoxide as a primer or solvent

Dimethyl sulfoxide (DMSO) is an organic sulfur compound with low surface energy, making it an effective solvent to facilitate polymerization during adhesive bonding [9, 22, 35]. DMSO enhances bond strength and durability by stabilizing the collagen matrix, inhibiting MMPs, and optimizing dentin moisture content [35]. Studies have demonstrated that incorporating DMSO into wet bonding protocols significantly improves the long-term stability of the adhesive bond [35].

VI Substrate treatment with lasers before adhesive bonding methods

Two of the most commonly used lasers are Er:YAG (Erbium-doped Yttrium Aluminium Garnet) lasers and plasma-based lasers. The Er:YAG laser induces specific topographical changes on the dentin substrate surface by removing the smear layer, evaporating water and organic content, and creating crater-like alterations [6]. These changes effectively increase the surface area available for bonding, which is critical for achieving durable adhesion [32, 36]. Laser irradiation has also been shown to have positive effects on dentin exposed to oxidizing agents [37]. Plasma lasers improve bond quality and stability over time, particularly during aging. Their mechanism of action involves generating carboxyl and carbonyl groups on the dentin surface, which enhances wetting and facilitates better monomer interaction [6, 38–40].

Synthesis of Current Knowledge and State of Investigations

Adhesive dentistry continues to evolve driven by advancements in both chemical and physical techniques. While chemical methods, particularly those involving natural agents, have been extensively investigated, physical techniques remain underexplored but exhibit considerable potential for further development.

A comparison of chemical agents and techniques reveals that each offers unique benefits and challenges. Chemical approaches, such as collagen cross-linkers and proteinase inhibitors, effectively strengthen the collagen matrix and inhibit enzymatic degradation, making them valuable tools for enhancing the biochemical stability of adhesive bonds. CHX and EDTA are particularly valuable due to their established clinical use, widespread availability, and ease of application in dental practice. Conversely, remineralization agents aim to enhance the mechanical and structural integrity of the bond by promoting natural dentin repair processes. Despite their potential, these agents often require extended treatment times and controlled conditions, which can be challenging to achieve in clinical settings. Physical techniques, such as laser treatments, offer a novel approach by inducing topographical changes on the dentin surface, thereby increasing the bonding area and improving adhesion strength and stability. Although promising, laser-based methods are limited by factors such as the cost, equipment accessibility, and the need for practitioner expertise. The most effective strategy for achieving the bond between restorative materials and dental tissues lies in the synergistic application of the various agents and techniques. For instance, combining collagen cross-linkers with laser treatments could optimize both chemical stability and physical adhesion of the bond.

This synthesis underscores the need to diversify research efforts, placing greater emphasis on physical techniques, particularly laser-based methods, while continuing to explore the use of chemical agents.

Conclusion

Current knowledge and experimental research demonstrate that modern methods for dentin substrate modification significantly enhance the initial adhesive bond. Collagen cross-linkers and proteinase inhibitors play a pivotal role in improving bond stability, while antioxidants and remineralization agents offer protection against degradation. Furthermore, modifications in adhesive techniques and laser treatments contribute to bond strength but require careful clinical application. The optimal approach to achieving long-lasting resin-dentin bonds involves a tailored combination of these methods. However, the degradation of the interfacial contact surface remains a persistent challenge that compromises the longevity of restorations.

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Rad je primljen 17. II 2024.
Recenziran 4. X 2024.
Prihvaćen za štampu 4. X 2024.
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