Dental Materials 41 (2025) 141–158

Contents lists available at ScienceDirect

Dental Materials

journal homepage: www.elsevier.com/locate/dental

The evolution of adhesive dentistry: From etch-and-rinse to universal bonding systems

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ARTICLE INFO

Keywords:
Hybrid layer degradation
Universal adhesive systems
Matrix metalloproteinases
Dentin collagen
Dentin biomodification

ABSTRACT

Objectives: This review aimed at presenting the mechanisms and pitfalls of adhesion to enamel and dentin, advances in the materials science and in the development of strategies to improve hybrid layer (HL) longevity.
Methods: Search of the literature was performed on PubMed, Scopus and Web of Science with keywords related to the structure of the dental substrate, HL degradation mechanisms and strategies to contrast them.
Results: Albeit the advances in the dental materials' properties, HL degradation is still a relevant and current issue in adhesive dentistry. However, adhesive materials have become more resistant and less operator sensitive, and good adhesion is currently in the hands of every practitioner. Numerous novel strategies are being developed, able to improve the resistance of adhesive resins to degradation, their ability to infiltrate and chemically bond to dentin, to remove the unbound/residual water within the HL, reinforce the dentin collagen matrix, and inhibit endogenous metalloproteinases. Many of the strategies have turned to nature in search for powerful biomodifying compounds, and for the inspiration as to mimic naturally occurring regenerative processes.
Significance: Extensive knowledge on the structure of the dental substrate and the complexity of adhesion to dentin has led to the development of improved formulations of dental adhesives and numerous valid strategies to improve the strength and longevity of the HL. Nevertheless, for many of them the road from bench to chairside still seems long. We encourage practitioners to know their materials well and use the strategies readily available to them.

1. Introduction

The advent of adhesive systems has revolutionized restorative and prosthetic techniques in dentistry, aligning with the principles of minimally invasive dentistry. These innovations facilitated more conservative approaches, allowing for the preservation of tooth structure and improved clinical outcomes.

Over the years, the evolution of adhesive systems has paralleled the in-depth investigation of dental substrates, examining their distinct characteristics and critical issues [1]. This research has been instrumental in understanding how different substrates interact with adhesive systems, ultimately enhancing the effectiveness and durability of dental restorations [2,3]. Concurrently, advancements in the field of biomaterials have significantly contributed to the development of more versatile and reliable universal adhesive systems and resin cements.

In the past two decades, research has focused on two main fronts: simplifying materials to reduce operator variability and identifying materials and approaches that stabilize the hybrid layer (HL) and inhibit factors compromising the long-term interfacial integrity.

Regarding the first aspect, the introduction of so-called "universal" materials currently represents the evolution of adhesive systems and cementation techniques [4,5]. These materials are highly versatile for both the operator and the adhesive substrates [6–8]. However, the terminology "universal" is still quite speculative for current adhesive materials, since they are not universally applicable in all different clinical scenarios. The operators need to have adequate knowledge of the

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https://doi.org/10.1016/j.dental.2024.11.011
Received 24 August 2024; Received in revised form 20 November 2024; Accepted 27 November 2024
Available online 4 December 2024

instructions for use and the nature of the adhesive substrate as to make adequate choices regarding the modality of use of adhesive materials and obtain the most durable and reliable outcome in each clinical situation [9].

For the second aspect, various compositions and techniques have been investigated over time to stabilize the HL. This includes the introduction of adhesive materials more resistant to hydrolysis, improvement of impregnation and chemical bond of the substrate with adhesive materials, removal of unbound water from the HL and the inhibition of endogenous enzymatic activity using chemical agents and physical approaches [10–14]. These methods are increasing in number, effectiveness, biocompatibility, and clinical applicability.

This review aims to explore the mechanisms and pitfalls of dental adhesion as well as the advancements in the dental materials and strategies designed to contrast them, highlighting the key developments and their impact on modern dental practices.

2. Adhesive systems

The traces of the beginning of the "adhesive era" can be found in the early 1950s when many researchers and clinicians put their efforts into developing materials that would provide micromechanical and, ideally, additional chemical interaction with dental tissues. Today we are marking nearly 7 decades of adhesive dentistry which set its basis on early findings [15–17] reported by clinicians and researchers without whom modern adhesion and, consequently, esthetic dentistry would not have developed. The list of scientists contributing to the development of early adhesive materials is long [18] and it would be somehow unfair to fail mentioning pioneers such as I.H.R. Kramer, O. Hagger, M. Buonocore, and R.L. Bowen [19,20] whose ideas and concepts are still relevant today. One of such widely accepted concepts remains acid-etching of enamel in order to provide predictable clinical outcome, regardless of the adhesive system used [21]. Similarly, although their chemical compositions are constantly being improved, Bowen's resin (Bis-GMA), as well as Hagger's functional glycero-phosphate dymethacrylate (GPDM) monomer remain important components in modern adhesive systems, despite the current trend to replace Bis-GMA with ''bio-safer'' materials [22].

Initially, adhesive systems were classified into generations [18]; however, this classification can be confusing and was largely used by dental industry to emphasize the latest trends in material production. Consequently, another classification taking into consideration adhesive's interaction with the smear layer was proposed. Accordingly, 2 groups of adhesive systems can be distinguished: etch-and-rinse (EAR) and self-etch (SE) systems [23–25]. This classification remains well accepted up to today.

2.1. Etch-and-rinse (EAR) adhesive systems

Common characteristic of all EAR systems is the use of 32–37 % phosphoric acid on enamel and dentin surface, followed by a thorough water rinse step to remove it from the tooth surface. This strong acid removes the smear layer from the enamel surface and demineralizes superficial layer of enamel, thus exposing enamel prisms [26]. Similarly, dentin etching removes the smear layer, exposes the organic matrix and makes it permeable for the adhesive resin application [2].

A 3-step version of EAR systems was the first to be developed and contains primer in a separate bottle. The application of primer facilitates the penetration of the third part of the system - the hydrophobic adhesive resin, eventually leading to the creation of a HL [3]. These materials, among which the most investigated one is OptiBond FL (Kerr), are considered as the "gold-standard" or the "reference" adhesive for many researchers due to its excellent clinical behavior in longer follow-up periods (over 25 years) [5]. A 2-step EAR system represents a simplified version since primer and hydrophobic resin have been incorporated into a single product [26]. The average thickness of HLs created by EAR adhesives may be product-dependent, varies on the application technique and dentin characteristics, and measures on average between 3 to 7 μm [27–32]. It is worth mentioning that the reported thicknesses of HLs may be influenced by the scanning-electron microscopy analysis preparation techniques (i.e. dehydration procedure and artifacts due to microscopy vacuum). Confocal laser scanning microscopy can therefore be a valid complementary method for assessing the HLs' thickness due to its non-destructive nature [33–36]. A summary of benefits and drawbacks of EAR systems is given in Table 1.

2.2. Self-etch (SE) adhesive systems

Unlike EAR, SE (or etch-and-dry) systems can bypass a separate acid-etching step since they contain acidic monomers, and they simultaneously etch dentin and penetrate the collagen network. SE adhesives can come as 2-step or 1-step systems, depending whether a primer and adhesive resin are provided separately or incorporated into a 1-bottle product [37]. Even though they contain acidic monomers, their etching potential to enamel is limited, thus making a preliminary enamel etching with phosphoric acid an obligatory step when using these systems [5]. The micromorphology of adhesive-dentin interface depends on the adhesives' acidity. Ultra-mild systems (pH $>$ 2.5) can interact with and demineralize the dentin surface only superficially (few hounded nanometers). The interaction depth increases to approximately 1 μm (mild SE approach, pH ~2), 1–2 μm (intermediately strong SE approach, pH between 1 and 2), and several micrometers deep (strong SE approach, pH $\leq$ 1) [38]. A major progress was achieved by including functional monomers, such as phosphate, phosphonate and carboxyl groups [39], which can either demineralize or chemically bond to hydroxyapatite through adhesion-decalcification concept [40]. A more complex version of SE systems, a 2-step SE adhesive such as Clearfil SE Bond (Kuraray), is also considered as "gold-standard" due to similar characteristics mentioned earlier for a 3-step EAR adhesive. An overview of SE adhesives' characteristics is shown in Table 2.

Table 1
Benefits and drawbacks of EAR systems.

Benefits	Drawbacks
Well-proven efficacy for long-term follow-ups (>20 yrs) with low annual failure rates (3.1 %).[5]	Technique sensitive: possibility of dentin over-etching (>15 s) and incomplete infiltration of the adhesive into the etched dentin.
Best approach for durable adhesion to enamel with complete smear layer removal and micromechanical interlocking.	Poorer behavior of 2-step EAR systems in *in vitro scenario*[19,27]; emerging evidence suggests that there may be no difference in clinical outcome between gold-standard 3-step EAR and simplified adhesive systems.[28]
Possibility to apply separately resin-free/poor hydrophobic adhesive resin in a sufficient thickness which may provide stress-absorbing potential.[5]	Bond-strength of EAR systems is influenced by the degree of dentin moisture in laboratory studies[29,30]; recent clinical evidence suggests that degree of dentin moisture may not have a crucial effect on longevity and post-operative sensitivity when posterior composite restorations are placed with a 2-step EAR system.[31]
Minor saliva contamination of dentin does not necessary reduce bond-strength in vitro.[19]	Solvent air-dry time should often be extended.
No higher risk for developing post-operative sensitivity compared to SE systems.[32]	HLs may be prone to leakage and enzymatic degradation.[5]
A 3-step "gold-standard" EAR adhesive shows minimal interfacial gap formation, regardless of the application mode (1 or 2 layers).[33]	Besides micromechanical interlocking, only some EAR adhesives might establish chemical bonding with intact dentin below the HL[34]. *In vitro* studies employing dentin barrier systems indicate potentially greater cytotoxicity for EAR systems.[35,36]

Table 2
Benefits and drawbacks of SE adhesive systems.

Benefits	Drawbacks
Less technique sensitive as their application on dentin does not require etching and rinsing step.	Insufficient etching potential to enamel.
Long-track record for 2-step SE adhesives (>20 years) with low annual failure rates (2.5 %).[5]	Some 1-step may compromise polymerization kinetics of self- or dual-cure resin-based materials.
Chemical interaction with dentinal substrate.	1-step HEMA-free SE adhesives are prone to phase separation in laboratory settings.[31]
Less vulnerable to biodegradation due to partial dentin demineralization and less exposure of collagen fibers.	
Clearfill SE Bond was proven to be non-cytotoxic in the dentin-barrier model.[32]	
1-step HEMA-free SE adhesives demonstrate comparable clinical behavior to a 3-step gold-standard EAR adhesive over the period of 14 years.[33]	

Table 3
Benefits and drawbacks of UAs systems.

Benefits	Drawbacks
Excellent clinical performance for follow-up period of up to 5 years and can be comparable to a more complex 3-step EAR systems.[40]	The lack of data from randomized clinical trials regarding behavior of UAs in longer term period (>10 years).
Some UAs can be applied in the "no-waiting" technique with acceptable clinical results when compared to conventional application methods (rubbing and/or waiting), providing they are used in EAR and SEE mode.[41]	The necessity to etch enamel as to provide predictable clinical outcome questions UAs' claimed versatility.[34,42]
No need to apply an additional layer of bonding resin to achieve optimal clinical behavior in non-carious cervical lesions.[43]	Low thickness can enable oxygen to impair polymerization efficacy of the adhesive layer.
2-step HEMA-free UAs have favorable bonding properties in the challenging high C-factor class-I cavity model and are comparable to that of the gold-standard 3-step EAR and 2-step SE adhesives.[44]	Necessity to additionally apply flowable composite layer over a 1-step UA in the high C-factor cavity model as to compensate bonding effectiveness.[44]
Applying 10-MDP-containing adhesives to subgingival margins may be safe for the periodontal tissues.[45]	UAs may exhibit material-dependent cytotoxicity and can trigger immune response when exposed to human dental pulp cells.[46]
	In vitro studies reported possible phase separation of UAs that are HEMA-free.[47]
	Potential negative influence of HEMA on nanolayering of the functional 10-MDP monomer.[48,49]

2.3. Current status of simplified adhesive protocols: universal adhesives (UA)

Universal, or multi-mode adhesive systems were launched to the dental market more than a decade ago and represent dental industry's attempt to simplify chair-side workflow without jeopardizing clinical efficacy of restorations whose integrity lies on HL formation. According to dental manufacturers, UA can be used in EAR, SE and selective enamel etching (SEE) mode – depending on clinicians' preference and they can also be indicated for managing dental (hyper)sensitivity [41]. Being less technique sensitive compared to traditional EAR and SE adhesives, in other words having the possibility to apply them on dry or moist dentin without significant impact on bond strength values and the ability to chemically interact with hydroxyapatite due to incorporation of functional monomers [42], made researchers and clinicians accept the term "universal" [43]. The adjective "universal" is furthermore justified by frequent inclusion of the most effective 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) monomer into UAs' formulation and the possibility to prime various substrates (ceramics, composites, metal alloys) [44]. When applied on unetched dentin, self-assembled 10-MDP-Ca salts are formed during the so-called "nanolayering" process [36] which may be responsible for higher bond-strength values observed in 10-MDP containing compared to 10-MDP free adhesives [45,46]. Alternative functional monomers to 10-MDP such as dipentaerythritol penta acrylate monophosphate (PENTA-P), glycero-phosphate dimethacrylate (GPDM), 4-methacryloxyethyl trimellitic acid (4-MET), and 4-methacryloyloxyethyl trimellitate anhydride (4-META) can be identified in UAs' formulations [1].

Initially argued as "single bottle self-etch adhesive for other application modes" [47], UAs have undergone a dynamic evolution of chemical composition due to their broad spectrum of indications (L Breschi. Changing operative mindsets with universal adhesives and cements. *Oper Dent* 2024; *In-Press*). Table 3 outlines advantages and limitations of UAs. Although blending some ingredients, such as chlorhexidine (CHX) [48], into a 1-bottle product may enhance bonding performance of UA's, the incorporation of silanes, on the other hand, may reduce bonding efficacy [1]. In order to maintain stability of commonly incorporated silane agents (i.e., 3-(aminopropyl) triethoxysilane and γ-methacrylo xypropyltriethoxysilane), a higher pH value is also required as to maintain their stability and this in return can decrease the etching capacity of the adhesive itself [1,5]. For this reason, some manufacturers have developed quadra functional monomer technology featuring novel Acid-Resistant Silane Coupling Agent (ARS) [49] which should be more resistant to acid degradation and prolonged storage (data retrieved from patent literature). Another interference among UA's components that should be mentioned is the one between silane agents and 10-MDP, as the former can cause hydroxylation of zirconia and alter the adsorption of 10-MDP, thus emphasizing the importance of optimizing the ratio of silane incorporated within UAs' formulas [50].

3. Dentin structure

3.1. Tooth structure

Tooth is a complex tissue, with main hard tissue components being enamel and dentin. What distinguishes teeth from other mineralized tissues of the body is that the tooth tissues lost to caries or trauma do not regenerate. The pulp has certain compensatory mechanisms in response to physiological and pathological stimuli, promoting the formation of secondary and tertiary dentin. However, irreversibly lost tooth tissues can only be restored using the available dental materials. The interaction of tooth tissues with the adhesive resins is dictated by their composition and differs greatly between enamel and dentin [51]. Enamel is primarily a mineralized tissue, (96 wt% mineral content, 4 wt % organic content and water) organized into prisms, while dentin contains more organic matter (70 wt% mineral content, 20 wt% organic content, 10 wt% water) [52–55], and its distinct morphological feature are the dentinal tubules which extend throughout its depth and help form the dentin-pulp complex.

Enamel was shown to be an excellent substrate for adhesion, forming reliable and durable resin-dentin bonds after etching with 32–37 % phosphoric acid for 30 s. This procedure results in a partial removal of mineralized tissue and the increase in the surface area in contact with the adhesive resin. A very important point determining the success of bonding to enamel is the fact that it can be thoroughly dried, enabling capillary attraction of the hydrophobic resin in the porosities created after etching [56,57].

On the other hand, the presence of tubular liquid, the higher organic content and the complex structure of dentin organic extracellular matrix

can affect the bonding properties of adhesive resins to dentin [51,56]. In the next paragraphs we will provide an insight into the structure of the dentin extracellular matrix as to better understand the difficulties related to dentin bonding, and the underlying reasons for the development of particular strategies for its improvement. .

3.2. Dentin collagen matrix structure

The dentin organic matrix is an important player is establishing adhesion and its durability since it is exposed after the etching step for EAR adhesive systems. Conversely, if an SE approach is used, the organic structure remains partially embedded within the residual mineral. The dentin extracellular matrix is primarily composed of collagen type I, making up 90 % of its structure. Each collagen molecule consists of three amino acid strands: two α1 strands and one α2 strand. These strands individually form a left-handed helix and then intertwine into a right-handed triple helix, creating the collagen molecule [58,59]. The triple-helical region makes up for over 95 % of the molecule, with the remaining 5 % being non-helical regions, specifically the carboxyterminal (C-terminal telopeptide) and aminoterminal (N-terminal telopeptide) regions [60]. Collagen molecules aggregate into fibrils by aligning along their long axes, separated by a 67 nm gap [61]. Inter- and intra-molecular cross-links connect these molecules, with the C-terminal region of one molecule reacting with the N-terminal region of another, enhancing the resilience of dentin collagen. Consequently, it remains intact even after 15 s of acid etching with 35–37 % phosphoric acid, a treatment that would damage dermal collagen [62,63]. However, over-etching (Fig. 2) can alter the structure of collagen molecules and proteoglycans (PGs), necessitating careful control during dental procedures [62,64,65]. Dentin collagen, once degraded, cannot be replaced as it does not regenerate [66].

Although collagen molecules are crucial to the extracellular matrix, the non-collagenous proteins, that form the remaining 10 % of the extracellular matrix, namely PGs, enzymes, and phospholipids also have important roles in dentin structure and stability. Collagen fibrils link perpendicularly with non-collagenous proteins, particularly PGs [67,68]. PGs consist of a core protein, glycosaminoglycans (GAGs), and linkage proteins, which help maintain the 3-dimensional structure of collagen fibril bundles [69,70]. Additionally, PGs play a role in dentin mineralization and regulate collagen's water affinity by organizing water molecules, which is vital during bonding procedures [63–65]. The 3-dimensional interactions within the extracellular matrix have been studied and visualized using selective immunolabeling techniques [63,71,72]. The selective removal of PGs or GAGs from the organic dentinal matrix impaired tensile strength of dentin collagen and made it more susceptible to degradation, demonstrating also detrimental effects on dentin bonding [73,74].

4. Degradation of the hybrid layer (HL)

If by definition HL is formed through the interaction of adhesive resins and dental substrate, its degradation certainly needs to be conditioned by the properties of each component separately, as well as their interaction, with particular attention on the surroundings they are in, or rather, the humid oral environment, prone to temperature, mechanical, microbial and enzymatic challenges. Between the two components of the HL, a "passive" and an "active" interaction can be obtained. The main goal of the adhesive resin is to penetrate adequately and embed completely the underlying substrate, in case of dentin, the demineralized extracellular collagen matrix. This would be the passive interaction of the adhesive resin with the dentin, which is naturally difficult being dentin collagen hydrophilic and adhesive resins hydrophobic. Hydrophilic monomers have been added to the formulations of these adhesives, that certainly improved the dentin hybridization but have brought about issues with the polymerization efficacy and resistance to hydrolytic degradation [75].

Functional monomers have been a breakthrough in the adhesive dentistry, introducing chemical, "active" component to resin-dentin bonding [1]. Nevertheless, at the bottom of the HL, the embedding of the collagen fibrils is often incomplete, leaving them denuded and surrounded by water. This exposes the collagen fibrils to degradation by endogenous proteases and enables the penetration of the water further into the HL, causing plasticization of the adhesive resin and mechanical strain on the fibrils. Electron microscopy studies suggest that collagen degradation might occur before resin loss [3]. The mechanisms of degradation of each component of the HL will be presented in the following paragraphs.

4.1. Degradation of the adhesive resin component of the HL

Adhesive resins are a blend of hydrophobic monomers, predominantly dimethacrylates, hydrophilic monomers, most often hydroxylethyl methacrylate (HEMA), in recent adhesive formulations very often functional acidic monomers that in certain cases can replace HEMA, photoinitiators, solvents (predominantly ethanol, acetone and water), and other additives [1]. It is of utmost importance that these constituents are stable and non-reactive among each other, which is not necessarily always the case. It has been demonstrated that the adhesive resins used after the recommended expiration date deteriorate in terms of their bonding properties, exhibit higher nanoleakage and activation of endogenous enzymes [76]. Moreover, it has been reported that also adhesives within their shelf life deteriorate due to the hydrolysis of the ester portion in the monomers [46]. In the EAR wet bonding technique, the adhesive comes into contact with the waterfilled collagen matrix, and hence, hydrophilic monomers are necessary to enable the adequate

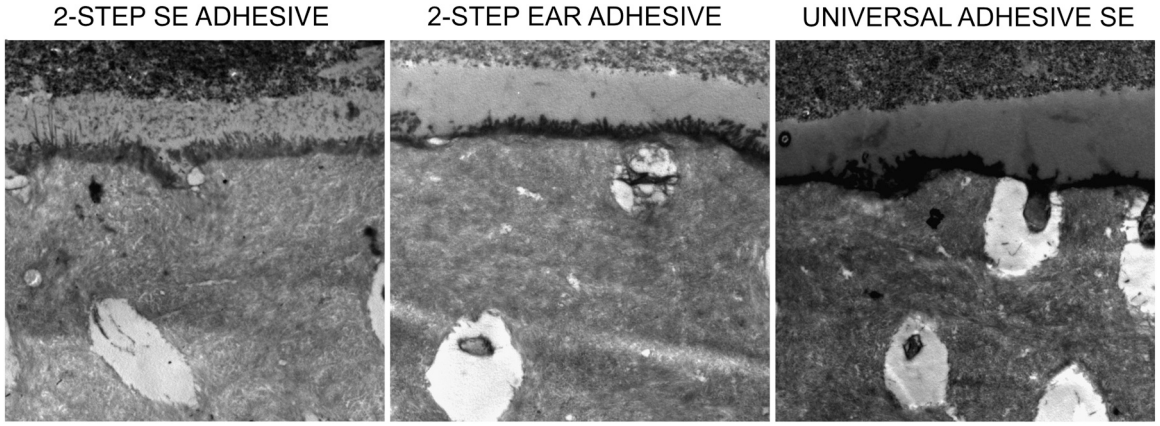

Fig. 1. Transmission electron microscopy images of dentin restored with different adhesive systems (2-step self-etch adhesive system, 2-step etch-and-rinse adhesive system, and a universal adhesive used in self-etch mode). D – dentin; A – adhesive layer; HL – hybrid layer; arrows – collagen fibrils within the hybrid layer.

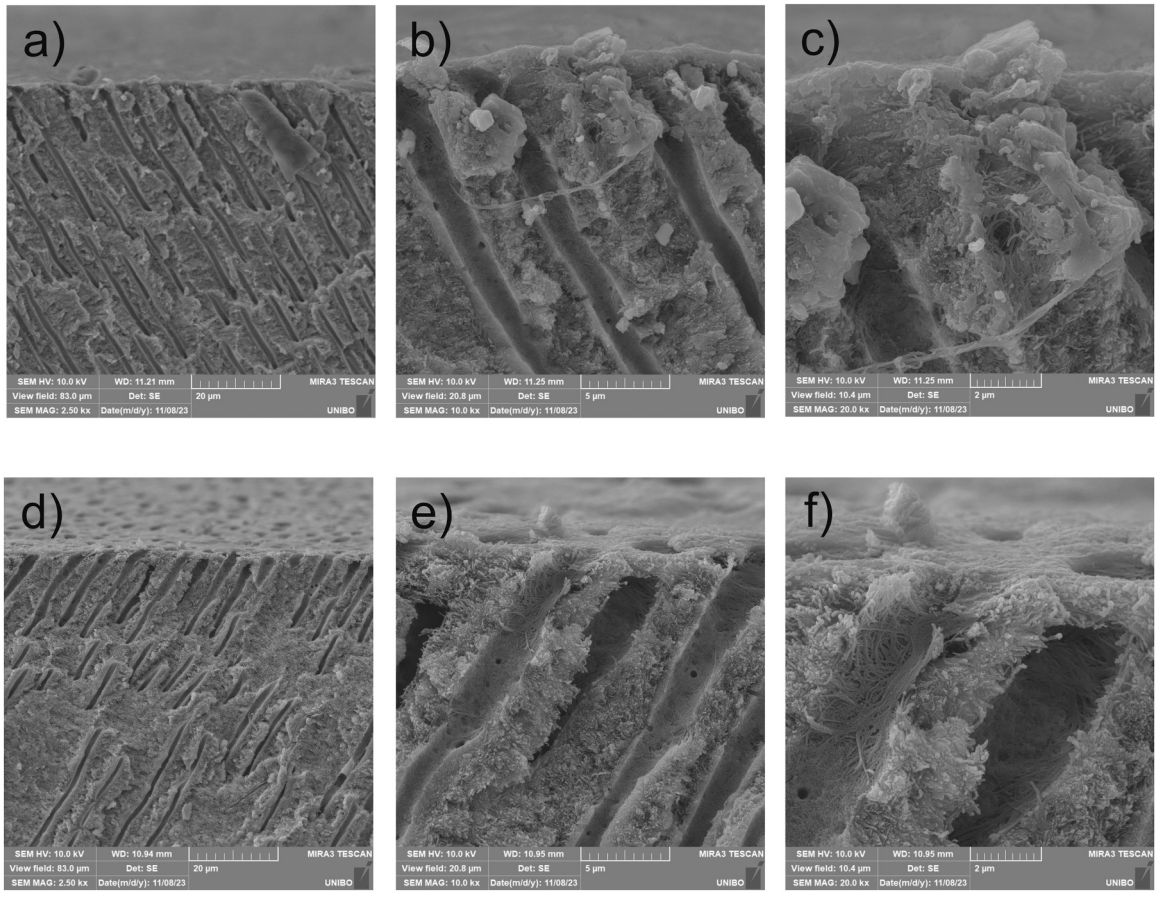

Fig. 2. Scanning electron microscopy images of dentin etched with a 35 % phosphoric acid gel for 15 s (a, b, c) or 60 s (d, e, f), fixated, dehydrated in ascending concentrations of ethanol and coated with gold/palladium. While after 15 s of acid etching there is a slight widening of the entrance into the tubules (~5 μm depth), a more pronounced widening of the tubules and a deeper penetration of the etchant (~10 μm) is noted after 60 s of etching. a, d: 2500x, bar size 20 μm; b, e: 10.000x, bar size 5 μm; c, f: 20.000, bar size 2 μm.

penetration of the adhesive resin into this substrate. After the polymerization, the adhesive resin should ideally be thermally stable and insoluble. However, there are several pitfalls related to this notion. The hydrophilic domains of the HL (usually placed closer to the bottom of the resin-dentin interface since they are the ones that can penetrate deeper into the hydrophilic collagen network) allow for a diffusion of the water through this layer [77,78]. Hydrophilic monomers are more prone to swelling and hydrolytic degradation, continuing the vicious cycle possibly initiated by collagen degradation [2,79]. The degraded monomers leach out of the HL, enabling the surrounding water to enter further into it and create the so-called water trees that have been revealed by means of the nanoleakage. This technique entails the exposure of the hybrid layer to particles of silver, which can penetrate the spaces where the water was present and can later be visualized under an optical or scanning electron microscope [80,81]. The further the water penetrates the HL, the larger surface of the adhesive resin is exposed to the hydrolytic degradation, softening and plasticization [10, 82]. But not only hydrophilic monomers are prone to degradation. Although hydrophobic monomers are more resistant, they indeed can degrade under the same circumstances after a prolonged exposure time, particularly with the water, lysozyme, amylases, carbonic anhydrases, peroxidases and other constituents present in saliva, along with the temperature changes and different pH insults present in the oral cavity [83]. It has been demonstrated that also polymer networks made from hydrophobic dimethacrylates are prone to hygroscopic and hydrolytic events after 6 months, with triethyleneglycol-dimethacrylate (TEGDMA) being more susceptible to sorption compared to Bis-GMA, which was more susceptible compared to urethane dimethacrylate (UDMA) [84], due to their ester, ether urethane and hydroxyl groups [83]. Furthermore, the evaporation of the solvent from the adhesive resin is nearly always incomplete, impairing the polymerization efficacy, as they do not form a network with the monomers in the adhesive, reducing the physical properties of the adhesive and resistance to degradation [85–87]. Moreover, in early formulations of adhesives that contained a mixture of hydrophilic and hydrophobic monomers, and only camphorquinone as the polymerization initiator, the polymerization of the hydrophilic portion was inadequate, causing a nanophase separation between the monomers of different hydrophilicities [88]. Other issues that arise by the loss of resin is the further denuding of collagen fibrils and exposure to solubilization and degradation promoted by the endogenous MMPs, and also the leaching of the unreacted monomers/release of degradation products, that can have adverse biological effects [89].

4.2. *Degradation of the dentin collagen matrix within the HL*

Unlike previously believed, Pashley et al. revealed that dentin collagen fibrils can be degraded in water without microbial involvement, due to the activity of endogenous dentinal enzymes [90]. Given that neither of the bonding modalities offers complete infiltration of the collagen matrix, there is always a layer of water-rich denuded collagen fibrils at the bottom of the resin-dentin interface [91,92], prone to hydrolytic degradation by host-derived enzymes.

Regarding the endogenous dentinal enzymes, the most prominent groups in terms of the influence on extracellular dentin matrix stability are the matrix metalloproteases (MMPs) and cysteine cathepsins (CTs).

MMPs, which are Zn^{2+} and Ca^{2+} dependent proteases, are involved in various physiological and pathological processes in dentin [93]. They contain a catalytic domain, a prodomain, and minor domains that dictate the interaction with the substrate [94]. These proteases are secreted in an inactive form and can be activated by dissociating the cysteine residue from the Zn^{2+} in the active site, replaced by water molecules [95]. Out of the 23 representatives of this family of enzymes, several, such as gelatinases MMP-2 and MMP-9, collagenase MMP-8, matrilysin MMP-7, stromelysin MMP-3, and enamelysin MMP-20, have been identified in dentin by means of biochemical and immunochemical assays and are believed to play roles in tooth development, mineralization and degradation processes [96–102].

MMPs can degrade nearly all components of the extracellular collagen matrix, but true collagenases (MMP-1, −8, −13, −18) specifically degrade collagen [94]. They cleave collagen at well-established sites, producing thermally unstable ¼ and ¾ fragments that other proteases can further degrade [103]. The key to collagen degradation is removing protective telopeptides to allow collagenases to cleave the triple helix [104]. The C-telopeptides sterically block the position where collagenases would bind to the triple helix, protecting the collagen molecule from cleavage by the MMPs. Enzymes that remove telopeptides in dentin are mainly MMP-2 and −9 [103], and are therefore pivotal for the degradation of the organic dentinal matrix. The expression and activity of these gelatinases have been extensively investigated. By means of immunolabeling, MMP-2 and −9 were found to be intrinsic constituents of the extracellular matrix [96], indicating MMPs as an important factor in the degradation of the HL, and the consequent failure of composite restorations. Further, gelatin zymography of proteins extracted from dentin powder precisely identified the pro- and active forms of MMP-2 and −9 [105]. Moreover, it was demonstrated that EAR as well as SE adhesive systems can activate dentinal MMPs, both by direct dentin powder treatment (non-polymerized adhesive resins) in gelatin zymography, and after the simulation of the clinical restorative procedure (polymerized adhesive resin and resin composite placement over a dentin section) by means of in situ zymography [106–108]. The activity of the MMPs is regulated by tissue inhibitors of metalloproteinases (TIMPs), and a tight association of TIMP-1 with MMP-2 and MMP-9 was demonstrated in human dentin using co-immunoprecipitation/immunoblotting analysis [109].

Apart from MMPs, CTs, particularly cathepsins K and B, are also significant in dentin's organic matrix and can degrade the dentin collagen matrix [97]. Cathepsin K, in particular, is a versatile enzyme that can cleave collagen at multiple positions, including helical and non-helical parts [110]. CTs have been demonstrated in dentin by means of immunohistochemical analysis [111], and may play an important role in caries progression and bone remodeling and collagen degradation during an orthodontic treatment [97]. They are more abundant in chronic carious lesions, possibly indicating their role in the promotion of growth factors secretion and consequent stimulation of odontoblasts. Interestingly, the activity of cathepsin K is regulated by GAGs (chondroitin 4-sulfate, or chondroitin 6-sulfate), with some activating and others inhibiting cathepsin K [112,113]. This demonstrates the complexity and the fine balance between the constituents of the extracellular dentin matrix, that can be disrupted by extrinsic and intrinsic stimuli.

MMPs and CTs can work synergistically to degrade collagen, creating a cascade that leads to HL degradation [114,115]. Hence, there are two main pathways for collagen degradation: one involves MMPs fragmenting collagen into ¼ and ¾ fragments that other proteases further degrade, and the other involves CT-GAG complexes degrading collagen independently [113].

5. Strategies to reduce HL degradation

As can be seen from previous paragraphs, preventing collagen degradation improves HL integrity, reduces nanoleakage, and enhances bond strength durability [116,117]. Therefore, it seems paramount to improve the collagen matrix hybridization, reinforce the collagen matrix and inhibit degradation by endogenous enzymes. From previous notions it is clear that water is the nemesis of the longevity of the HL, impairing hybridization of collagen fibrils, reducing polymerization efficacy and inducing hydrolytic degradation of both collagen fibrils and adhesive resin. Water is an integral component of any biological system, and its influence cannot be fully eliminated, especially in the oral environment. However, it is possible to manage the presence and distribution of water in key moments in the dentin-resin adhesive procedures, that could significantly reduce, or at least postpone the negative influence of water on HL longevity. Hence, the strategies to prevent the degradation of the HL aim to achieve one or more of the following objectives:

1) Improve the hybridization of the collagen fibrils by adhesive resins;
2) Improve the resistance of adhesive resins to hydrolytic degradation;
3) Improve polymerization of adhesive resins;
4) Improve the chemical bond strength between dentin substrate and adhesive resins;
5) Biomodify and reinforce the dentin collagen matrix;
6) Inhibit endogenous dentinal enzymes;
7) Remove the unbound/residual water.

Often, strategies to prevent HL degradation cover more than one of these objectives. In the following paragraphs we will present different strategies established in the literature.

5.1. Self-etch or etch-and-dry bonding technique

It has previously been described that exposed collagen fibers are better embedded in SE adhesives compared to EAR adhesives [62,118–120]. Two-step SE adhesive systems could be considered "etch--and-dry" bonding systems since unetched dentin is dried before applying the SE primer, and after self-etching with a designated primer, no water rinsing is employed. The primed dentin is dried and sealed with a solvent-free adhesive. These primers contain acidic monomers such as 10-MDP in higher concentrations than those previously used for wet-bonding adhesives. Water is added to these primers only in sufficient amounts to allow for ionization of acidic monomers and to solubilize dentin's mineral phase. These water concentrations are proprietary but generally range from 20–25 vol% [121], a fraction significantly lower than the 70 vol% [122] water present in acid-etched dentin just prior to adhesive application. Furthermore, the primer is air-dried to evaporate water and leave the monomers in place that will pave the path for the hydrophobic monomers present in the adhesive resin.

5.2. Immediate dentin sealing (IDS)

IDS [123], whose origins can be traced in the beginning of the 1990s [124], is a technique that has been increasingly advocated among clinicians who reported that it can improve prognosis of adhesively cemented indirect restorations and reduce initial postoperative sensitivity (POS) [125]. Although a chronological overview of the literature may reveal evolution and different variants of the IDS technique (Fig. 3), the concept of the originally proposed technique remains unchanged: immediately after a tooth has received preparation for an indirect restoration, a layer of an adhesive system is applied to the freshly cut and exposed dentin and then polymerized [123]. Unlike conventional delayed dentin sealing (DDS) where the adhesive is applied during cementation procedure, the application of the adhesive in the IDS technique protects the dentin from contamination with various provisional materials, bacteria and saliva [124]. Furthermore, the application and polymerization of the adhesive within the freshly exposed dentin allows dentin's optimal hybridization and prevents collapse of collagen fibrils, eventually leading to stronger hybrid layers and improved

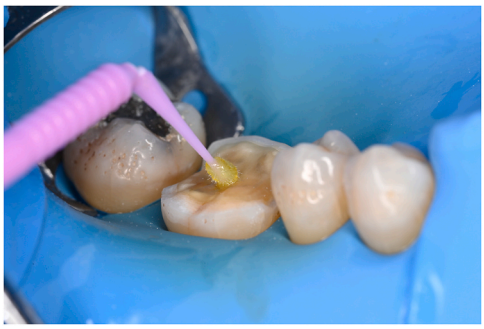

Fig. 3. Image of clinical application of the immediate dentin sealing technique immediately after the preparation of the tooth for an onlay restoration.

bond-strength compared to DDS technique [126]. Moreover, the advantages of the IDS technique include alleged reduced post-operative sensitivity (POS), better marginal adaptation of the indirect restoration [127] and a more homogeneous adhesive interface between the adhesive agent and dentin/restorative material [128].

A "gold-standard" 3-step EAR adhesive (Optibond FL, Kerr) was initially indicated for the IDS technique; however, a 2-step SE or even recently introduced universal adhesive systems can also be valid alternatives to seal the dentin in case practitioners prefer to leave it unetched [129,130]. The choice of an adhesive system has a direct influence on the clinical steps performed during the IDS technique: when applying an unfilled or lightly filled adhesive (universal and some SE adhesive systems), a layer of flowable resin coating should be placed immediately after application and polymerization of the adhesive (the so-called "reinforced IDS"). Reinforcing the thin adhesive interface with a layer of flowable composite protects it from oxygen inhibition and it also prevents removal of the IDS adhesive layer during cleaning of the provisional material [130]. On the other hand, applying a protective layer of flowable composite with a 3-step EAR system is optional, since IDS layer created by this filled adhesive is resistant to air-abrasion with aluminum oxide and phosphoric acid etching employed during cleaning phase [130]. Although many in vitro studies have reported beneficial effects of performing the IDS technique [131], these findings should be extrapolated to clinical settings with caution, as a recent systematic review [132] reported that IDS has no influence on the POS occurrence. Considering the low number of the studies included in the mentioned review, alongside with their risk of bias analyses, it becomes apparent that strong evidence from randomized clinical trials regarding the IDS technique still lacks and should be thoroughly investigated in future [133].

5.3. Ethanol wet bonding

Adhesive formulations containing dimethacrylates capable of creating highly linked resin polymers are usually dissolved in ethanol to ensure the mixture is in a single phase, since most dimethacrylates are extremely poorly soluble in water, and could undergo phase changes when mixed with water [134]. Ethanol-solvated adhesive resin placement on water-saturated acid-etched dentin could result in microscopic phase changes in the applied adhesive. To resolve this issue, ethanol wet-bonding technique was proposed by Pashley et al. [135] who replaced rinse-water with ethanol, which has resulted in excellent bond strength of hydrophobic adhesives to dentin [136]. When ethanol-solvated adhesives are placed on ethanol-saturated dentin, phase separation does not occur, and residual water percentage in the resin-dentin bonds is decreased [137]. In this way, a better hybridization of dentin organic matrix is ensured. This initiates a cascade of desirable consequences, such as that the collagen that is well hybridized and protected from the water is less prone to MMPs induced degradation, and the hydrophobic resins resist the hydrolytic degradation as well [138,139]. However, this technique had limitations, such as long time necessary for execution, which would not be clinically feasible. It has later been demonstrated that also application of ethanol for 1 min can offer benefits in terms of adhesion properties [140]. However, ethanol wet bonding cannot remove the bound water withing the collagen fibrils [141]. It was demonstrated using molecular dynamic computer simulations which recreated the three layers of bound water in collagen matrices that only 50 % of the bound water in the outermost layer of bound water could be replaced by ethanol [142].

5.4. Dimethyl sulfoxide (DMSO) primer

DMSO, with low surface energy and the ability to form stable complexes with water and create "hydrophobic water", facilitate radical polymerization reactions in dental adhesion [143,144]. It can be dissolved in water, several organic solvents, as well as resin monomers, making it rather versatile for use in dentistry. Studies show that it increases immediate and long-term bond strength and reduces dentin collagen matrix degradation [120,145–148], possibly due to improved dentin wettability and adhesive penetration and forming hydrogen bonds with proteins [149]. DMSO may also inhibit MMPs [150].

5.5. Cold atmospheric plasma treatment (CAP)

CAP is an ionized gas that produces oxygen and nitrogen species (RONS) which can cause biological effects on the substrate [151]. Apart from the chemical effects, there can also be electromagnetic and thermal effects [152]. It can be applied as a direct or indirect treatment. For instance, it can be used to "activate" liquids or hydrogels and be used for tissue regeneration. It has also been shown to have a cytotoxic effect on cancer cells while preserving healthy cells [153,154]. In restorative dentistry it has been applied to decrease the surface tension and increase the wettability of dentin by adhesive resins, increasing bond strength [155,156]. Furthermore, CAP direct treatment as well as CAP-activated liquids can either increase or decrease the MMPs activity, depending on the duration of the treatment, composition of the liquid, etc. (internal data from our laboratory).

5.6. Acrylamides for dental applications

As already mentioned, the bonded interface is subjected to several challenges, including ones extrinsic to the tooth (e.g., bacterial colonization, saliva-derived hydrolytic and enzymatic degradation), as well as others intrinsic to the tooth (e.g., HL degradation by dentin-derived MMPs). In particular for methacrylate-based materials, which are the most commonly used in today's clinical practice, labile ester bonds are particularly prone to degradation by simple hydrolysis at low pH, and/or by the action of esterases derived from the saliva and biofilm [157,158]. In spite of their many advantages and familiarity by practicing dentists, the past several years have seen significant and growing interest in developing ester-free monomers for restorative materials [159], including epoxy-based [160], thiol-ene [161], alkyne-azide [162,163], vinyl-sulfones [164,165], vinyl-ethers [166], and acrylamides [167,168]. While most of these materials have been successful in demonstrating reduced degradation in vitro, their commercial adoption must overcome hurdles such as cytotoxicity concerns, need for specialized photopolymerization schemes, or underwhelming mechanical properties [159,169,170]. One such chemistry that has gained attention in the past several years, including with commercial examples, are multi-acrylamide-based materials [171]. This is not a new idea, as many examples of such monomers exist for dental applications in the literature [172–174]. However, their utility as a component of restorative composite is limited by their poor mechanical properties after water storage [175], which stems from the fact that acrylamides are in general more hydrophilic than methacrylates such as TEGDMA [176]. For adhesives, though, where the mechanical requirements are not as high, and

hydrophilicity is in fact a great advantage, some encouraging results have been published in recent years. While it is important to acknowledge that commercial adhesive materials using methacryl- and acrylamides exist, it must also be pointed out that these examples use non-crosslinkable, mono-functional monomers [177,178], for which clinical performance has not shown advantage in relation to the conventional methacrylate-based materials [179,180]. In turn, at least in vitro, multi-acrylamide monomers have been demonstrated to achieve up to a four-fold increase in microtensile bond strength stability after 6 months storage in water [175], and after being tested under physiologically-relevant conditions combining bacterial and mechanical challenge in a bioreactor [169]. This has been partially ascribed to their greater than 90 % stability at pH as low as 1–2 [175]. However, given the high hydrophilicity of these monomers, even compared with HEMA [159], the monomer stability alone cannot explain the improved bond strength and interfacial integrity preservation observed in those previous studies. More recently, potential direct collagen reinforcement has been investigated, and in fact increased dentin shear modulus and reduced hydroxyproline production have been reported for samples treated with these monomers [181]. It has been speculated that acrylamides might be able to establish covalent and/or supra-molecular bonds with collagen [181,182]. For example, cobalamine, an amide-rich, cobalt-coordinating compound, has been shown to reinforce collagen through a complex mechanism, involving secondary intermolecular interactions such as hydrogen bonding [183]. Others have demonstrated amide-π interactions that stabilize the collagen triple helix in self-assembling systems [184]. One caveat of those results, however, is that acrylamides are not as reactive as methacrylates [168], and therefore, necessitate a three-component initiator system including some iodonium salt and co-polymerizations with dimethacylates [171, 185]. Even still, the partial elimination of ester linkages, and the full elimination of the mono-functional HEMA from the composition, has rendered HLs with greater bond strength values and improved stability compared with the conventional counterparts.

5.7. Increasing polymerization efficiency

Like all resin materials, adhesive systems achieve their final properties through a polymerization process. This process involves the conversion of carbon-carbon double bonds in the monomers into carbon-carbon single bonds, linking monomers together to form long chains and interchain crosslinks, resulting in a stiff and strong polymer [186]. In light-curing materials, polymerization occurs when adhesive monomers are exposed to a photo-curing light of adequate output and the correct wavelength, which should align with the absorption spectrum of the photoinitiator (usually camphorquinone) included in the adhesive. When light cannot reach the resin monomers, a chemical-activated reaction (self-curing) can be employed. Dual-curing materials allow for a combination of both photo- and self-curing polymerization [187]. The degree to which monomers convert into polymer determines the length of the polymer chains, which directly affects the final strength of the material. During the polymerization of dental adhesives, achieving effective cross-linking between hydrophilic and hydrophobic monomers is crucial for a strong adhesive layer [186].

Suboptimal polymerization, often seen in simplified adhesive systems that contain higher amounts of hydrophilic monomers, results in reduced mechanical properties, making these systems more prone to hydrolytic degradation [188]. Water can become trapped within the adhesive layer during photopolymerization, and its presence at the tooth/adhesive interface may lead to suboptimal polymerization of the adhesive monomers [189]. This can increase permeability within the hybrid layer [190]. Additionally, the co-presence of hydrophilic and hydrophobic domains can lead to nano-phase separation, resulting in non-homogeneous layers and lower conversion rates of hydrophilic monomers due to incompatibility with hydrophobic photoinitiators [191]. Proper polymerization is thus crucial for adhesive strength and stability. Factors such as the adequacy of light exposure during curing and the compatibility of monomers with photoinitiators influence polymerization quality.

Numerous studies indicate that recommended exposure times are insufficient for optimal polymerization, necessitating longer durations. Using a light source with sufficient radiant exitance and extending exposure times beyond manufacturer recommendations can enhance the degree of conversion and reduce the permeability of simplified adhesives, thereby improving their in vitro performance. However, it's crucial to monitor temperature increases to avoid potential harm to the pulp, especially when utilizing high-power curing lights. To mitigate heat buildup, air-cooling or breaks between prolonged exposures are recommended [187].

Camphorquinone (CQ), the most common photo-initiator, has hydrophobic properties that may hinder the conversion of hydrophilic monomers. To address these issues, alternative hydrophilic photoinitiators, such as Norrish type I initiators (including acyl phosphonates and bisacylphosphine oxides), have been suggested. For example, TPO (a combination of ethyl 4-dimethylaminobenzoate and diphenyl (2,4,6-trimethylbenzoyl)-phosphine oxide) has shown promise in improving the degree of conversion (DC) and stability of hydrophilic adhesive systems by reducing phase separation [192,193]. Studies indicate that TPO enhances the DC of adhesives without significantly affecting dark cure reactions compared to CQ. Other photoinitiators like bis(acyl)phosphine oxide (BAPO) and phenylpropanedione (PPD) have also been shown to improve DC in adhesive systems [194]. Additionally, a borate-based system has been introduced in some commercial self-etch adhesives, showing high DC values under experimental conditions, although its mechanism is not fully understood [195].

The priming components of dental adhesive systems often include organic solvents, such as water, ethanol, and acetone, to enhance wettability and facilitate the infiltration of adhesive resins into dentin. These solvents can comprise up to 50 % of some formulations [196]. While water and ethanol are hydrophilic and promote interaction with dentinal moisture, acetone helps to remove water from the dentin. However, any residual solvent that is not adequately evaporated prior to polymerization can negatively impact the adhesive layer. Since solvents are non-polymerizable, they can interfere with the polymerization process, acting as plasticizers that weaken the adhesive's physical properties [186] Although solvents decrease viscosity and improve resin infiltration, excessive concentrations can reduce the degree of conversion due to increased distances between reactive radicals during polymerization [85].

The ideal concentration of solvent for optimal polymerization often conflicts with the concentration needed for the best physical properties of the adhesive. For instance, while a small amount of residual ethanol (10–20 %) can enhance conversion, it may also compromise mechanical strength. Residual water can also lead to phase separation, hindering proper curing [197]. Complete solvent removal is crucial for effective polymerization, as nonvolatile monomers mixed with solvents can reduce evaporation efficiency. Therefore, the optimal solvent concentration must be tailored to each adhesive formulation. To improve solvent evaporation, manufacturers recommend air-drying times of 5–10 s, although longer drying times and the use of warm air can enhance bond strength and hybrid-layer homogeneity [186] Ultimately, sufficient polymerization is essential to offset any adverse effects of incomplete solvent evaporation, and extending light exposure times can further improve conversion and reduce permeability [198,199].

5.8. Chemical bonding of monomers to dentin collagen

Chemical bonding of monomers to dentin collagen and at the same time the copolymerization with other monomers from the adhesive resin would offer an optimal "bridging" between two ends of the HL and improve its longevity. Recently it was demonstrated that 10-MDP can form chemical bonds not only with the Ca ions from hydroxyapatite, but

also with the dentin collagen. Hydrogen bonds are formed between the phosphate group of the functional monomer and the nitrogen group of dentin collagen molecules. Apart from 10-MDP, other functional monomers, such as PENTA [200] and bis[2-(methacryloyloxy)-ethyl] phosphate, were shown to bind to collagen chemically [201,202]. The number of hydrogen bonds can vary based on the different monomer structure, possibly due to the compatibility of the three-dimensional conformation of the monomer and collagen molecules. The presence of hydrogen bonds was concomitant with higher initial bond strength in the groups treated with functional monomers. However, a decrease in bond strength was noted after aging [200], with a decrease in hydrogen bonding, probably due to the degradation of the collagen fibrils at the bottom of the hybrid layer that could not be completely stopped. Another novel monomer, isocyanate-terminated urethane methacrylate precursor has the ability to form covalent and hydrogen bonds with collagen via its -NCO group that bonds to the -NH_2 group in dentin collagen [203]. It also has curable double bonds, enabling copolymerization with other adhesive monomers. This collagen reactive monomer demonstrated a decrease in the degradation rate of the HL and in the gelatinolytic activity [204]. Attempts have also been made to functionalize a methacrylate monomer with grape seed extract, with promising results in terms of resistance of collagen to degradation and the ability to copolymerize with other monomers [205]. Other research groups have also found inspiration in the nature, aiming to test the N-(3, 4-dihydroxyphenethyl)methacrylamide (DMA), a monomer inspired by mussle adhesion property to wet substrates. This monomer successfully decreased the rate of dentin collagen matrix and resin-dentin interface degradation, while increasing bond strength, possibly due to hydroxyl groups of DMA that cross-link to collagen [206,207].

5.9. Calcium-chelation dry bonding

This technique takes advantage of the fact that molecules with molecular weights under 600 Da can penetrate the collagen, whereas those larger than 40 kDa are excluded [208–210]. Phosphoric acid, with a molecular weight of 100 Da, is small enough to diffuse throughout the collagen fibrils, solubilizing both the extra- and intrafibrillar minerals, which results in the complete demineralization and softening of dentin. Applying a calcium chelator with a large molecular weight would only remove the apatite minerals from the extrafibrillar space, creating interfibrillar spaces that allow inward diffusion and uptake of monomers into the hybrid layer, resulting in bond strength preservation over time. This has been reported after the use of sodium polyacrylate [211] as well as an experimental etchant – EDTA conjugated to glycol chitosan (size >40 kDa), with a preservation of bond strength and HL integrity after artificial aging, and a clear advantage over phosphoric acid [212,213]. Since the collagen fibrils remain fully mineralized, they are stiff enough to avoid shrinking or collapsing when the residual rinse water is evaporated with strong air blasts. These procedures enable "dry bonding" using hydrophobic resins similar to those used in pit-and-fissure sealants [211]. Additionally, these processes do not activate matrix proteases, and since no residual water remains, proteases would not have the conditions needed to become active.

5.10. Dentin biomodification

One of the widely investigated strategies to reduce the degradation of the HL is the reinforcement of the demineralized dentin collagen matrix. This can be achieved by synthetic or natural cross-linkers, molecules that can form inter and intrafibrillar chemical bonds that seem to be irreversible [214]. The chemical interaction of different cross-linkers to dentin collagen occurs via distinct mechanisms [215]. Treatment with cross-linkers was demonstrated to enhance the mechanical properties of dentin and reduce the susceptibility to hydrolytic degradation promoted by host derived proteases.

Aldehydes are mostly used as fixatives and have antimicrobial properties. Glutaraldehyde crosslinks dentin collagen by chemically bonding via its two aldehyde groups with the ε-amino groups of hydroxylysine and peptidyl lysine residues of the collagen molecule [216]. Glutaraldehyde was shown to enhance the mechanical properties of demineralized dentin collagen matrix [217–219], increase the resistance to degradation [215,220], and even to promote dentin remineralization [221]. Glutaraldehyde pretreatment was demonstrated to also enhance bonding properties of sound dentin [222] and to restore the mechanical and bonding properties of caries-affected dentin to the levels of sound dentin [215,223]. A controversy regarding the clinical use of glutaraldehyde is certainly posed by its cytotoxicity after direct application on the cells [222]. However, it was shown that when placed on the dentin barrier, glutaraldehyde 5 % was no longer cytotoxic. Hence, 5 % glutaraldehyde within a hydrophilic resin blend it has been approved for clinical use as a desensitizing agent, in several formulations. This agent has been demonstrated to improve bond strength of UAs to dentin [224]. Another representative of this group, acrolein, was also shown to improve long-term bond strength after a 1 min application at a very low concentration (0.01 wt%) [225].

Another group of synthetic cross-linkers of interest in the dental field are carbodiimides. The most investigated representative of this group is 1-Ethyl-3-[3- dimethylaminopropyl] carbodiimide Hydrochloride (EDC). EDC forms an intermediate product by reacting with the carboxyl group of the C-terminus of one collagen molecule, which further bonds to the amino group of the N-terminus of an adjacent collagen molecule, forming a stable covalent bond and releasing urea as a byproduct [226]. EDC was mostly investigated in form of a separate aqueous primer that was placed on demineralized dentin collagen scaffolds, or on dentin before the adhesive procedures, demonstrating increase in mechanical properties and protective effects against dentin collagen degradation [226–230], as well as against HL degradation after 6 months [231,232], 1 year [233,234], 5 years [235] (Fig. 4), and even 10 years of accelerated aging in artificial saliva at 37 °C (internal data from our laboratory). This effect was also confirmed in radicular dentin [236,237].

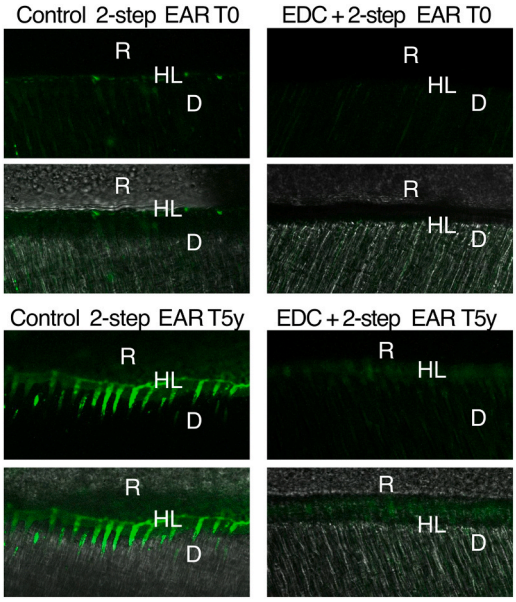

Fig. 4. Confocal microscopy images of dentin restored with a 2-step etch-and-rinse (EAR) adhesive and a composite resin subjected to the in situ zymography technique after 24 h or after 5 years of aging in artificial saliva at 37 °C. Briefly, specimens were glued to glass slides and ground down, covered with a fluorescein-conjugated gelatin, left overnight in humid and dark conditions and observed on a confocal microscope. The green fluorescence represents the relative level of activity of the dentinal matrix metalloproteinases. D – dentin; HL – hybrid layer; R – adhesive resin; T0 – observations after 24 h; T5y – observations after 5 years.

Moreover, treatment with EDC restored the mechanical properties of caries affected dentin. In an attempt to reduce the chairside time and number of steps in the adhesive procedures, different formulations of carbodiimides were investigated (N,N'-dicyclohexylcarbodiimide - DCC), that are soluble in ethanol and could therefore potentially be blended into an adhesive resin [238]. DCC demonstrated preservation of bond strength and reduction of interfacial nanoleakage.

In the tendency towards a more sustainable dentistry, as well as to decrease the potential cytotoxic effect of dental materials, natural plant derivatives have been proposed as dentin biomodifiers. Among them, polyphenolic compounds, such as proanthocyanidins, tannins, and curcumin [215,223,239–243] as well as chitosan [244–246] have a prominent role. Vast number of studies tackled the influence of these compounds on dentin biomodification. Proanthocyanidins react with dentin collagen primarily through hydrogen bonds, but also covalent bonds and hydrophobic bonds [247], at a molecular, microfibrillar and fibrillar level [248]. These cross-linkers are very potent, but there are difficulties regarding the standardization of the compounds extracted from plants, due to their vast variability in structural configurations even within a single plant [247]. These structural variations as well as the degree of polymerization influence their interaction with dentin. It was recently demonstrated that proanthocyanidins with a higher degree of polymerization are more effective in reducing collagen degradation and improving bond strength of adhesive resins to dentin [249]. Specifically, trimers and tetramers induced a more potent increase in dentin extracellular matrix mechanical properties compared to monomers, dimers and hexamers [248]. Similarly to other strategies, there has also been a tendency of developing proanthocyanidin complexes with other compounds as to potentially insert them directly into one of the materials used for dental adhesive procedures. Functionalization of hydroxyapatite nanoparticles with proanthocyanidins improved bond strength of caries affected dentin [250]. Also, biodegradable poly-[lactic-co-glycolic acid] nanoparticles were loaded with proanthocyanidins improved the mechanical properties and reduced the degradation of demineralized collagen scaffold, while enabling the formation of a homogenous hybrid layer. The addition of polylactide capsules containing proanthocyanidin into an experimental adhesive resin was demonstrated to preserve the HL and reduce infiltration after 2 years of artificial aging [251]. When grape-seed extract-functionalized methacrylate was blended into an experimental adhesive, it exhibited both collagen reinforcement against hydrolytic degradation, and the acceleration of the resin polymerization rate [205].

Another versatile abundantly available natural compound with broad utility in the field of dentistry is chitosan, mainly extracted from invertebrates, such as shells of crustaceans or insect cuticles [252]. In its native state it is only soluble in acidic pH, while it becomes soluble in water after its degradation into different oligomers [253,254]. Chitosan is a very versatile compound, with the ability to form complexes with other biomaterials or tissues through the primary and secondary hydroxyl groups and an amino group, demonstrating antimicrobial activity, dentin biomodification and anti-proteolytic properties [253,255]. Methacrylate-modified chitosan preserved long term bond strength when incorporated into an adhesive primer [256]. Moreover, impregnation of dentin collagen scaffold with carboxymethyl-chitosan improved further the efficacy of chemical and photoinduced cross-linking to improve the mechanical properties and reduce the degradation of collagen [257]. UVA-activated chitosan/riboflavin dentin cross-linking improved the mechanical properties of the collagen matrix, as well as bond strength to dentin [244,258]. However, note should be taken that the higher concentrations of chitosan had an adverse effect on adhesion, possibly causing impairment of adhesive penetration by occupying interfibrillar spaces. Chitosan nanoparticles contributed to the resistance of collagen to collagenase degradation by forming chemical complexes both with collagen and collagenases, forming polyanion–polycation complexes due to their different charges [246]. The variety of possibilities of chitosan application potential is clear from the previous lines. However, further research should be focused on in-depth analysis of different chemical profiles of chitosan and on a standardization of the formulations used in dentistry as to arrive from bench to chair-side.

An interesting feature of the cross-linkers is that apart from binding to collagen, they can also form chemical bonds with the MMPs, often resulting in conformational changes and active site blocking, causing permanent inactivation of the enzyme. This effect was demonstrated for numerous cross-linkers, such as aldehydes [225,242], EDC [226,235–237,259,260], proanthocyanidins [214,222,242,261,262], and chitosan [263,264].

5.11. Inhibition of the endogenous MMPs

After decades of research, it is beyond doubt that endogenous MMPs inhibition reduces degradation of the HL. Numerous inhibitors have been tested and developed, both those that have a specific affinity towards certain MMPs and cysteine cathepsins, and those who have a broad action against them.

The specific inhibitor of MMP-2 and −9, such as galardin incorporated into an EAR adhesive primer, has shown reduced hybrid layer degradation after 1 year [265], while the addition of SB-3CT, a specific inhibitor of MMP-2 and −9, into a SE primer did not influence bond strength [266]. Specific inhibitors of CTs, such as E-64 and odanacatib, inhibit these enzymes by binding to their cleavage sites, mimicking their substrates [267], though data on their effect on dentin bond durability is still limited [268].

The nonspecific MMPs and CTs inhibitors are to the most part cationic compounds that bind electrostatically to anionic sites on demineralized and native dentin and have chelating properties. The most investigated MMPs inhibitor, due to its availability in the daily clinical practice, is CHX. CHX is a cationic chelating agent, binding Ca and Zn ions, necessary for the MMPs activity. Although the CHX-dentin bond seems to be reversible, substantivity of CHX to both mineralized and demineralized dentin is rather high and lasts up to 8 weeks [269] and cannot be debound from dentin tissues by HEMA [270]. CHX can inhibit MMPs [271] as well as CTs [272], even in very low concentrations. It was demonstrated in vitro that CHX 0.2 % increases resin-dentin bond strength after 1 year [273–275], 2 years [116,276], and 5 years [277] of artificial aging, even after only 30 s of pretreatment time. This was also confirmed in radicular dentin [278]. Some reports claimed that CHX had a limited effect on the preservation of the HL possibly due to leaching [279,280]. Nevertheless, CHX could be detected in the HL even after 5 or 10 years of artificial aging, while inhibiting MMPs' activity and preserving its integrity (Fig. 5) [277,281]. A universal adhesive containing CHX showed better bonding performances and enzymatic silencing compared to a competitor not containing this compound [48]. The incorporation of 0.5–5 wt% CHX into experimental adhesives did not impair degree of conversion [282,284]. However, elastic modulus of the adhesive could be significantly affected [283]. Several *ex vivo* investigations also confirmed the beneficial effects of CHX in HL preservation in primary and permanent dentin [117,285–287], and a systematic review of in vitro studies confirmed long-term beneficial effects of CHX on HL longevity [288]. However, more long-term randomized clinical studies should be performed as to confirm these effects in a clinical setting [289].

Another chelating agent, with long history in dentistry is ethylenediaminetetraacetic acid (EDTA), utilized in endodontic therapy for root canal enlargement. EDTA removes Ca^{2+} from collagen matrices and binds Zn^{2+} from the catalytic site of MMPs [290,291]. However, this agent has several drawbacks, including a lengthy application time and the reversibility of its effects due to water solubility [292].

Another group of inhibitors positively charged at physiological pH are quaternary ammonium compounds. One such compound, benzalkonium chloride (BAC), a mixture of alkylbenzyl-dimethylammonium chlorides with various alkyl chains, has been tested as an MMP

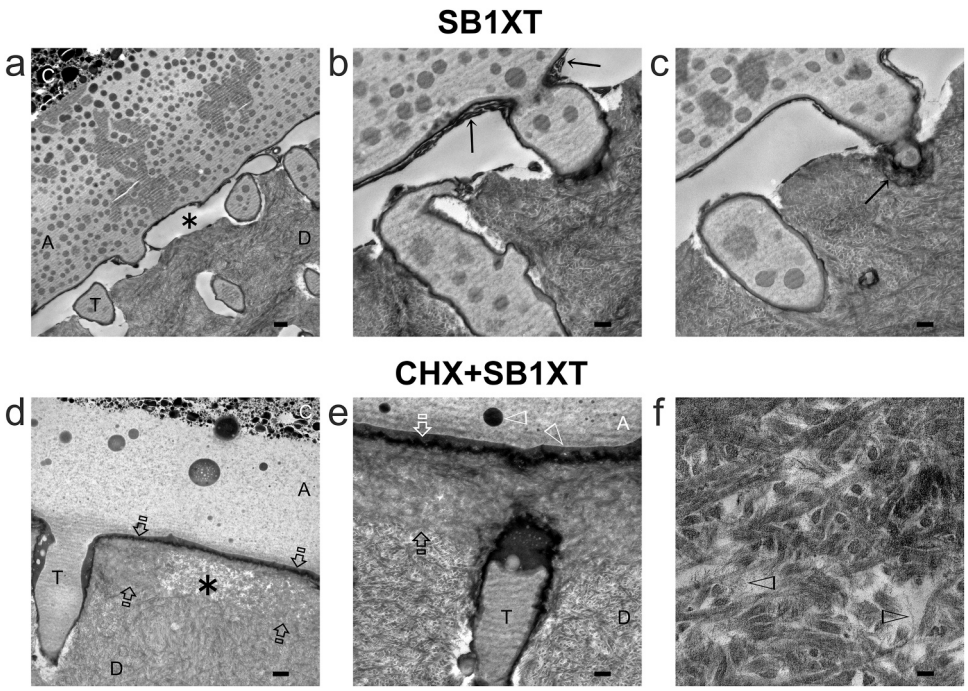

Fig. 5. Transmission electron microscopy (TEM) images showing the resin-dentin interface. Samples were fully demineralized and then stained while intact, after being stored in water for 10 years. **Top row**: Samples bonded with a 2-step etch-and-rinse adhesive without a chlorhexidine (CHX)-containing separate primer (SB1XT). **Bottom row**: Samples bonded with a CHX-containing separate primer (CHX + SB1XT). **Scale bars**: (a) 1 μm; (b) 500 nm; (c) 500 nm; (d) 1 μm; (e) 500 nm; (f) 100 nm. **Symbols**: **Asterisk** – Fully (a) or partially (d) degraded collagen fibrils within the H; **Black arrows** – A thin layer of collagen remaining at the top (b) and bottom (c) of the partially degraded H; **Open arrowheads** – (e) represent the polyalkenoic acid copolymer component of the adhesive; (f) show a high magnification of the region marked by an asterisk in (d), where collagen fibrils have unraveled and degraded into microfibrils. **Abbreviations**: **H** – hybrid layer; **D** – intertubular dentin; **T** – dentinal tubule; **A** – adhesive; **C** – resin composite. Reprinted with permisson from Breschi et al. [283].

inhibitor. BAC strongly binds to demineralized dentin and has demonstrated an immediate inhibitory effect comparable to CHX [293]. When blended into the formulation of commercial universal adhesives in the concentrations of 0.5 % and 1 %, BAC demonstrated lower activity of the MMPs compared to the control group [294,295]. However, its bonding properties were different when blended into different universal adhesives. One research group demonstrated better bonding properties of the BAC-doped adhesive [295-297], while another reported a detrimental effect on bond strength over time, possibly due to the impairment of the degree of conversion or physical properties of the adhesive resin [294]. Incorporating methacrylates into these compounds (quaternary ammonium methacrylates, or QAMs) seems to enhance their efficacy and enables blending of these inhibitors into adhesive resins [298]. One QAM, methacryloyloxydodecylpyridinium bromide (MDPB) has already been incorporated into a commercial adhesive system (Clearfil Protect Bond, Kuraray Noritake Dental Inc., Osaka, Japan) with claims that it can copolymerize with methacrylates in the adhesive resin and also inhibit the MMPs activity [299,300]. Following the good results obtained with MDPB, other QAMs were investigated as MMPs inhibitors with mixed outcomes. For instance, different concentrations of QAM-enriched adhesive blends showed an increase in degree of conversion, but a concentration dependent decrease in the mechanical properties of the experimental adhesives [301]. Another QAM-blended formulation demonstrated protection of dentin collagen matrix against degradation comparable to CHX [302]. Recently, bis-quaternary ammonium salts-based di-methacrylate monomers were developed and reported to have superior antimicrobial activity compared to MDPB [303].

Moreover, pharmaceutical agents used for various medical conditions have also been shown to inhibit MMPs through chelation. For example, tetracycline and its analogs, doxycycline and minocycline, have demonstrated inhibitory effects on collagenases and gelatinases [304–306]. Doxycycline loaded into Halloysite® nanotubes and blended into an adhesive resin showed dose dependent anti-MMP and antibacterial properties without impairing the mechanical properties of the adhesive, bond strength or cell viability. [307,308]. Also, bisphosphonates, particularly polyvinylphosphonic acid, have produced good immediate results, though their long-term effectiveness remains uncertain [309].

5.12. *Biomimetic remineralization of the HL*

Indeed, a fascination of researchers in the dental field is to achieve perfect mimicking of the nature, in a tissue such as dentin that to date cannot be replenished once lost. Hence, a vast amount of research has been conducted on dentin remineralization. It was shown that without a biomimetic primer, remineralization of the dentin collagen scaffold resulted in a mere extrafibrillar deposition of minerals, without assuming the correct hydroxyapatite structure and without actually remineralizing the intrafibrillar space [310]. Therefore, biomimetic analogs need to be an integral part of the dentin remineralization process, as to assume the role of acidic non-collagenous proteins such as dentin matrix protein 1 (DMP1), dentin sialophosphoprotein (DSPP), bone sialoprotein (BSP), and osteopontin (OPN) [311]. Intra- and interfibrillar biomimetic remineralization technique has been presented by Tay and Pashley both of demineralized dentin matrices and of resin bonded dentin [312,313]. This technique entails the use of the Portland cement (as the source of calcium hydroxide) in simulated body fluid (containing phosphates) producing an amorphous calcium phosphate phase. Both polyacrylic acid and polyvinylphosphonic acid were necessary to assume the role of DMP1. Polyacrylic acid played a role in the formation of metastable amorphous calcium phosphate precursors in the nanoscale, while polyvinylphosphonic acid helped attract the precursors towards the collagen fibrils and guide the assembly of the nanocrystals into larger apatite platelets [312,313]. This protocol was further refined and investigated into depth and confirmed [310,314,

315]. As to render biomimetic remineralization clinically feasible, further research focused on investigating the possibility to apply the biomimetic analogs as separate primers during the adhesive procedures and then restore the dentin with a bioactive composite with a slow release of remineralizing agents [316,317]. These studies demonstrated efficient remineralization and preservation of bond strength after 3 months for the EAR adhesive system [317] and 6 months for the SE adhesive system [316]. An important point to consider is that remineralization not only reinforces the collagen matrices, but also "pushes back" the water stat surrounds collagen fibrils, preventing hydrolytic degradation, and inactivating MMPs [315]. Also, dentin remineralization is a process that takes several months to complete, and therefore the use of an agent that could inhibit the MMPs, or agents with both inhibitory and remineralizing properties during this period is essential, as to avoid that the dentin collagen matrices are degraded before they can be remineralized. Hence, compounds with both remineralizing and MMPs inhibitory properties could be a valid solution. For instance, copper-doped bioactive glass nanoparticles demonstrated remineralizing properties, reduced MMPs activity, increased cellular activity and increased bond strength [318]. Further, a zolendronate-containing primer in relation to an ion-releasing adhesive was shown to reduce MMP-induced collagen degradation [319]. Another strategy would be to "speed-up" the remineralization process. Recently, a rapid intrafibrillar mineralization protocol was proposed, which demonstrated intrafibrillar mineralization of dentin collagen in as low as 1 min or 10 min treatment with a solution containing amorphous calcium fluoride stabilized with polyacrylic acid [320].

6. Conclusions

As our understanding of the mechanisms and vulnerabilities of dentin adhesion continues to expand, strategies to enhance the quality and longevity of the HL are rapidly advancing. New formulations of dental adhesives and innovative biomaterials with multifaceted roles have been shown to improve dentin collagen hybridization, improve the mechanical and bonding properties of adhesive resins, protect collagen fibrils from enzymatic degradation, and inhibit endogenous enzymatic activity. While in vitro studies are abundant, only a few of these strategies have been integrated into clinical practice. Nonetheless, we strongly encourage practitioners to familiarize themselves with the underlying causes of resin-dentin interface failure, the properties and adequate use of adhesive systems, and to apply available strategies for preserving the HL. Long-term clinical studies are needed to evaluate these emerging strategies.

Funding

This study was financed by the European Union - NextGenerationEU through the Italian Ministry of University and Research under PNRR 2022 "Therapeutical effects of Cold atmospheric plasma in Head And Neck Cancer and oral hEalth preservation - C.H.A.N.C.E.?", cod: 2022ATYY5B sector LS7 (grant holder Lorenzo Breschi).

Declaration of Competing Interest

None.

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