Degradation of Resin-Dentin Bonded Interface: A Review

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Abstract

   Hybrid layer can be described as the resin impregnated demineralized dentin layer. It comprises of the adhesive resin and the collagen fibrils that serve as scaffold for resin infiltration. Degradation of the hybrid layer is one of the major investigated topics in the restorative dentistry. It occurs through the hydrolysis of adhesive resin and the breakdown of collagen fibrils by endogenous proteases especially matrix metalloproteinases (MMPs). Hydrolysis occurs when the water acts as medium for chemical bonds breakdown especially methacrylate based resin containing ester bond that is vulnerable for this process. MMPs are embedded in the dentin during tooth development. These enzymes are activated by acid during dentin demineralization of etch-and-rinse and self-etch adhesive system. Since adhesive resin infiltration is often incomplete, denuded collagen fibrils associated with water can be enzymatically digested, eventually contributing to the hybrid layer deterioration. This review describes the mechanism of hybrid layer degradation and the potential strategies to slow down this process.

Review (J Int Dent Med Res 2018; 11(2): pp. 537-542)

Keywords: MMPs, hydrolysis, degradation, hybrid layer.
Received date: 14 March 2018   **Accept date:** 02 April 2018

Introduction

   Contemporary dental adhesives can be categorized into etch-and-rinse (ER) and self-etch (SE) adhesives based on their interaction to dentin: removing (ER) and modifying smear layer (SE).[1, 2] Both systems involve removal inorganic component of enamel/dentin followed by applications of adhesive resins to fill the demineralized space and ultimately create the zone referred as "hybrid layer (HL)".[3] This hybridization consists of adhesive resins and the collagen network that is infiltrated with adhesive monomers. The durability of this layer is a key for determining the longevity of resin composite restorations. Unfortunately, resin composite restorations last approximately 8 years compared to that reported for amalgam restoration (11-12.8 years).[4,5] Secondary caries is one of the most reasons for replacement.[4, 6]

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   Ideally, the adhesive monomer is expected to fully impregnate into the demineralized dentin and create stable bond between dentin and resin composite. Regrettably, whether the different types of adhesive system or technique used for dentin bonding, studies have documented that the HL are not as durable as anticipated due to the degradation of both adhesive resin and collagen matrices in oral environment.[1,2,7,8] Over time, this phenomenon weakens the resin-dentin interface and leads to gaps formation between dentin and restoration[1] and may ultimately contribute secondary caries formation. Therefore, this review aims to provide an overview of the two unique mechanisms of HL degradation through hydrolysis of adhesive resin and dentinal collagen breakdown by MMPs and the strategies to stabilize the HL.

Incomplete resin infiltration into demineralized dentin

   The evidence of imperfect encapsulation of adhesive monomer is observed by nanoleakage studies in which the nanometer-sized molecules (e.g. silver nitrate) diffuse to demineralized dentin, adhesive resin, or the HL. It occurs possibly due to the fluid movement, the

anastomosis complex of dentin[9] or the continuous etching of the self-etch adhesive system.[10] Nanoleakage is a useful criterion for the evaluation of adhesive performance[11] and often found at the bottom of the HL. Even though these nano-scaled porosities ranged *circa* 20–200 nm do not permit bacterial penetration, bacterial products, water and enzyme may use the nanoleakage as a pathway for HL degradation of both adhesive resin by hydrolysis and denuded collagen fibrils by endogenous proteinases.[12,13] In addition, in vitro or in vivo experiments widely reported the reduction of resin-dentin bond strength after the long-term (6-12 months or longer) aging (i.e. water storage, thermocycling) which supports the deterioration of HL.[14-19]

Hydrolysis of adhesive resins

Dental adhesives are mainly consisted of methacrylate based monomers such as bisphenol Adiglycidyl ether diemthacrylate (Bis-GMA), triethylene glycol dimethacrylate (TEGDMA), urethane dimethacrylate (UDMA) and 2-hydroxyethyl methacrylate (HEMA). These monomers contain hydrolytically vulnerable functional groups: ester (R-CO-O-R), carboxyl (-COOH), hydroxyl (-OH), phosphate ($-PO_4^{3-}$) and urethane (R-NH-CO-O-R).[20,21] Generally, dental polymers are deteriorated in aqueous environment by two main mechanisms: passive hydrolysis and enzymatic degradation. Hydrolysis is defined as a chemical reaction in which bonds of molecules break down using water. Hydrolysis that is catalyzed by enzymes is called "biodegradation". It was reported that degradation of dental polymers occurs through oxidation, chain scission and attack of functional groups producing small molecules or degradation products.[21]

Human saliva contains esterase enzymes that can hydrolyze methacrylate dental monomers.[22] These enzymes are produced from bacteria[23], salivary glands[22], human cells (i.e. human gingival/pulp fibroblasts[24], monocytes and macrophages).[25] The esterase enzymes presented in saliva cause hydrolysis of methacrylate based monomers producing carboxylic acid (R-COOH) and alcohol (R-OH). For example, Bis-GMA is hydrolyzed to Bis-hydroxy-propoxy-phenyl-propane (BisHPPP) and methacrylic acid (MA, Figure 1) in aqueous

solution. The degree of hydrolytic or enzymatic degradation is related to the degree of conversion, crosslinked networks, formulation of monomer, and specificity and concentration of enzyme to the monomer. Finer and Santerre showed that Bis-GMA is more resistant to enzymatic hydrolysis by pseudo-cholinesterase than TEGDMA in a dose dependent manner.[26]

The enzymatic degradation adversely affects the resin-dentin bond strength, surface hardness, wear resistance[21] and fracture toughness.[27] Furthermore, Kermanshahi et al.[28] found that the exposure of resin bonded dentin specimens to esterase enzymes facilitates bacterial microleakage into dentin and contributes to the progression of secondary caries as the increased bacterial penetration depth was pronounced in the test group compared to the non-exposure group.

Once the dental resins are hydrolyzed and released their breakdown products [(i.e. BisHPPP, MA and triethylene glycol (TEG)], these degradation products also induces the human cells to release more esterase resulting in more leaching of byproducts andcreating vicious cycle.[24]

The interactions between breakdown products andoral bacteria were investigated. In vitro studies found that the byproducts of dental resins (i.e. BisHPPP, TEG, MA) can upregulate *S. mutans* specific genes such as gtfB, gtfC, gbpB (bacterial adhesion and biofilm formation related genes), comC and comD (quorum-sensing related genes), yfiV (a putative transcriptional regulator), leading to increased bacterial virulence and cariogenicity[29,30]. These findings suggest that degradation products can potentially contribute to reduced longevity of adhesively bonded restorations.
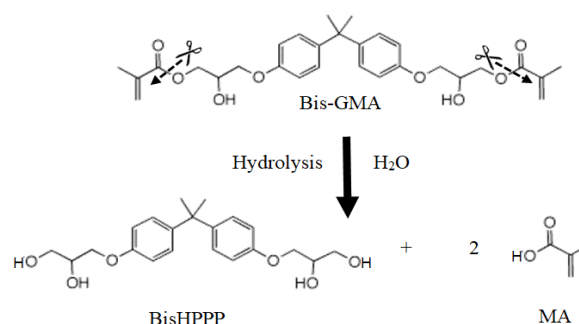
Figure 1. Hydrolysis of Bisphenol A glycidyl methacrylate (Bis-GMA) to Bis-hydroxy-propoxy-phenyl-propane (BisHPPP) and methacrylic acid (MA).

Degradation of collagen fibrils by matrix metalloproteinases and other proteases

Matrix metalloproteinases (MMPs) are a group of zinc dependent endopeptidases that are responsible for regulation of the components of extracellular matrix (ECM) especially type I collagen which is the main component of dentin matrices.[31] MMPs crucially participate in the physiological and pathological remodeling and destruction of living tissue such as arthritis, periodontal disease and tooth development. Based on their internal homologies and substrate specificity, MMPs are classified into six main classes as follows: collagenases, gelatinases, stromelysins, matrilysins, membrane-types, and other MMPs (Table 1).[31, 32]

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Collagenases	MMP-1 (collagenase-1)*
	MMP-8 (collagenase-2)*
	MMP-13 (collagenase-3)
Gelatinases	MMP-2 (gelatinase A)*
	MMP-9 (gelatinase B)*
Stromelysins	MMP-3 (stromelysin-1)*
	MMP-10 (stromelysin-2)
	MMP-11 (stromelysin-3)
	MMP-12 (metalloelastase)
Matrilysins	MMP-7 (matrilysin, PUMP-1)
	MMP-26 (matrilysin-2)
Membrane type (MT) MMPs	MMP-14 (MT1-MMP)*
	MMP-15 (MT2-MMP)
	MMP-16 (MT3-MMP)
	MMP-17 (MT4-MMP)
	MMP-24 (MT5-MMP)
	MMP-25 (MT6-MMP)
Other MMPs	MMP-18
	MMP-19
	MMP-20 (enamelysin)*
	MMP-21
	MMP-23
	MMP-27
	MMP-28 (epilysin)

Table 1. Classification of MMPs.
*indicated MMPs identified in dentin

MMP activity is controlled at the level of transcription, activation of zymogens (inactive MMPs), interaction with specific extracellular matrix component and inhibition of activated enzymes by tissue inhibitor of metalloproteinases (TIMPs).[33] Failure of their control can lead to several pathological conditions such as atheroma, arthritis, cancer and inflammation.[34,35] MMPs is

secreted as zymogen or inactive enzyme, and therefore, they have to be activated by proteinases, heat, low pH or other MMPs for their fully function.[36] The activation occurs through the "cysteine switch" mechanism where the bond between Zn^{2+} in the catalytic domain and the cysteine (-SH) in the prodomain of MMP structure is disrupted leading to the active MMPs (Figure 2). MMPs participate in dentin matrix formation during tooth development and secondary dentin formation. After collagen matrix calcification, the MMPs remain trapped within the mineralized dentin matrix and inactive.[2] Studies reported that odontoblasts can secrete MMP-2,-8,-9,-13,-20 and MT1-MMP.[37] So far, at least MMP-1,-2,-3,-8,-9,-20 and MT1-MMP have been identified in dentin.[36, 38-43]

MMPs have been suggested to be responsible for HL degradation.[1, 3, 44-47] Even though published studies demonstrated the presence and activity of endogenous enzymes in human dentin[39, 44, 48, 49], the direct evidence of MMP activity within the HL after acid exposure was firstly revealed in the in situ zymography.[40] It showed that the MMP activity was intense at the bottom of the HL where the exposed collagen occcured.[40] Interestingly, this observations also correspond to the area of interfacial nanoleakage which is the initial area of HL degradation. During the dentin pretreatment for dentin bonding, phosphoric acid or acidic primer etching in ER and SE adhesive systems is not only demineralized dentin for microretention, but low pH would also expose the collagen networks and activate matrix bound MMPs.
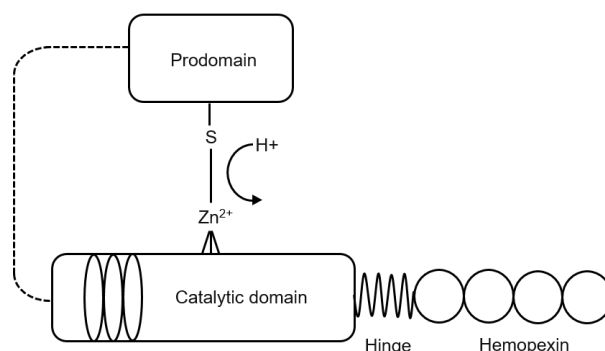
Figure 2. The activation of inactive MMPs. The bond between Zn^{2+} in the catalytic domain and the cysteine (-SH) in the prodomain of MMP structure is disrupted by acid (H+) leading to the active MMPs.

The active MMPs slowly degrade the exposed collagen fibrils (uninfiltrated by resin monomers)[50,51], weakening the resin-dentin bonds and reducing longevity of the resin restorations.

Cysteine cathepsins are a group of lysosomal cysteine proteinases. There are at least 11 human cysteine cathepsins (B, C, F, H, K, L, O, S, V, X and W).[52] Similar to MMPs, cysteine cathepsins take part in extracellular matrix degradation and remodeling. Unlike MMPs that work at neutral pH, most of cysteine cathepsins function at acidic environments except Cathepsin K that possesses gelatinolytic activity at pH 4.0–7.0 and collagenolytic activity at pH 5.0–6.5.[53] Human odontoblast can express a number of cysteine cathepsin gene.[54] To date, cysteine cat hepsin B and cysteine cat hepsin K are found in human dentin.[52] Cysteine cathepsin K is the only endopeptidase that is able to cleave multiple sites of the triple helix region of the collagen chain generating different fragments of collagen molecules. Similar to bacterial collagenases, this distinct property is not found in human MMPs as they can cleave collagen chain at one unique site.[52] These observation supports the possible role of cysteine cathepsins in HL degradation.

Strategies to preserve bonded interface

A number of approaches are introduced to overcome the deterioration of adhesive-dentin bonded interface including the modification of dentin bonding protocol (i.e. dentin pretreatment after acid etching), use of protease inhibitors, crosslinkers, chelating agents and a combined treatment.

Chlohexidine (CHX) is an MMP inhibitor that is extensively investigated in vitro and in vivo studies. CHX can be applied directly on demineralized dentin or can be incorporated into adhesive system (i.e. acidic primer, adhesive) either as a polymerizable chlorhexidine-methacrylate[55] or CHX solution.[56] Generally, the immediate dentin bond strength showed no significant different between 2% CHX and the control (without CHX) but the use of 0.2% CHX negatively affected the bond strength. After aging, the preservation of dentin bonding seems to be promising with CHX (0.2-2%) since CHX had higher bond strength compared to the control. However, this trend does not remain after long term aging.[45] Similarly, a clinical study on class V lesion with 2% CHX application using split-mouth design showed no long term advantage of CHX since restorations of the control (no CHX) started debonding after 6 months and the CHX treatment group was not debonded until 12 months.[57] These results correspond to other clinical studies.[58, 59]

Tetracycline derivatives are broad spectrum antibiotics with an MMP inhibitory effect though the Zn^{2+} chelating property. Doxycycline at subantimicrobial level incorporated into adhesive resin using aluminosilicate clay nanotube as a carrier showed potent MMP-1 inhibition without negative effect on physic-chemical properties of adhesive.[51] Similarly, application of 2% minocycline pretreatment on demineralized dentin significantly improved microtensile bond strength reduction and nanoleakage after 24 months of aging compared to the non-treated group.[60]

Crosslinkers such as carbodimide, glutaraldehyde, and proanthocyanidin strengthen the HL by forming the covalent bonds between collagen molecules, improving mechanical properties of dentin and making more resistant to degradation.[61] Proanthocyanidin has a dual function as a crosslinker and MMP inhibitor. Proanthocyanidin does not only improve the mechanical properties of dentin, but it can also stabilize the dental collagens against enzymatic digestion[62] possibly due to the induction of conformational change of enzyme structure[61] and the noncovalent nature of its interaction with collagen molecules.[63]

Gallardin, synthetic MMP inhibitor, exhibits a collagen-like backbone facilitating the binding to MMP active site on the catalytic domain of MMP structure resulting in MMP inhibition.[46] Treatment of gallardin reduced interfacial nanoleakage after 1 year aging compared to the no treatment group.

Polymerizable quaternary ammonium compounds (QAMs) such as 12-methacryloyloxydodecylpyridinium bromide (MDPB) significant decreased the loss of dry mass of the dentin beams incubated with QAMs (0.2–6.0% loss of dry mass) compared to the no QAMs group (29% loss of dry mass).[64] Moreover, the unique benefit of QAMs over other MMP inhibitors is the methcrylate-polymerizable property which makes the QAMs not leaching out of the bonded interface.

Finally, polyphenol compounds (i.e. green tea polyphenol epigallocatechin-3-gallate),

benzalkonium chloride, chelating agents (ethylenediaminetetraacetic acid, EDTA) and other MMP inhibitors have all been employed and demonstrated successful protease inhibition propertties.[47] However, although these strategies provides promising results, most of the inhibitor are not methacrylate polymerizable and will leak out to the environment after aging. Moreover, some inhibitors are reversible in nature (i.e. doxycycline, EDTA). Therefore, a long term inhibition may not be achieved unless the carrier is used for their sustained release. Thus, well-designed long term clinical trials (i.e. randomized clinical trial) has not been fully investigated and should be determined in the future.

Conclusions

Degradation of the HL is unavoidable. It reduces the longevity of the resin restoration. Indeed, studies have provided the strategies and clinical procedure to stabilize the resin-dentin interface. Although this review may not be addressed all available information, the key evidences are discussed. Further studies are needed on new knowledge, technique and invention to improve the stability of the adhesive bonded interface.

References

1. Breschi L, Mazzoni A, Ruggeri A, Cadenaro M, Di Lenarda R, De Stefano Dorigo E. Dental adhesion review: aging and stability of the bonded interface. Dent Mater 2008; 24(1): 90-101.
2. Mazzoni A, Tjaderhane L, Checchi V, et al. Role of dentin MMPs in caries progression and bond stability. J Dent Res 2015; 94(2): 241-51.
3. Porto IC, Nascimento TG, Oliveira J, Freitas PH, Haimeur A, França R. Use of polyphenols as a strategy to prevent bond degradation in the dentin–resin interface. Eur J Oral Sci 2018; 126(2): 146-58.
4. Van Nieuwenhuysen JP, D'Hoore W, Carvalho J, Qvist V. Long-term evaluation of extensive restorations in permanent teeth. J Dent 2003; 31(6): 395-405.
5. Mjor IA, Dahl JE, Moorhead JE. Age of restorations at replacement in permanent teeth in general dental practice. Acta Odontol Scand 2000; 58(3): 97-101.
6. Forss H, Widstrom E. Reasons for restorative therapy and the longevity of restorations in adults. Acta Odontol Scand 2004; 62(2): 82-6.
7. Mazzoni A, Angeloni V, Sartori N, et al. Substantivity of Carbodiimide Inhibition on Dentinal Enzyme Activity over Time. J Dent Res 2017; 96(8): 902-08.
8. Tjaderhane L, Nascimento FD, Breschi L, et al. Strategies to prevent hydrolytic degradation of the hybrid layer-A review. Dent Mater 2013; 29(10): 999-1011.
9. Hashimoto M, Fujita S, Endo K, Ohno H. Effect of dentinal water on bonding of self-etching adhesives. Dent Mater J 2009; 28(5): 634-41.
10. Wang Y, Spencer P. Continuing etching of an all-in-one adhesive in wet dentin tubules. J Dent Res 2005; 84(4): 350-4.
11. Mobarak EH, Daifalla LE. Long-term nanoleakage depth and pattern of cervical restorations bonded with different adhesives. Oper Dent 2012; 37(1): 45-53.
12. Sano H. Microtensile testing, nanoleakage, and biodegradation of resin-dentin bonds. J Dent Res 2006; 85(1): 11-4.
13. Lee T-Y, Cho B-H, Son H-H. The nanoleakage patterns of different dentin adhesive systems. J Korean Acad Conserv Dent 2003; 28(2): 169-77.
14. Garcia-Godoy F, Kramer N, Feilzer AJ, Frankenberger R. Long-term degradation of enamel and dentin bonds: 6-year results in vitro vs. in vivo. Dent Mater 2010; 26(11): 1113-8.
15. Abdalla AI. Effect of long-term water aging on microtensile bond strength of self-etch adhesives to dentin. Am J Dent 2010; 23(1): 29-33.
16. Favarao J, Zanini MM, Coelho Sinhoreti MA, et al. Immediate and 6-month Bond Strengths of Different Adhesives in the Oral Environment. J Adhes Dent 2017; 19(6): 475-81.
17. Sezinando A, Luque-Martinez I, Munoz MA, Reis A, Loguercio AD, Perdigao J. Influence of a hydrophobic resin coating on the immediate and 6-month dentin bonding of three universal adhesives. Dent Mater 2015; 31(10): e236-46.
18. Armstrong SR, Vargas MA, Chung I, et al. Resin-dentin interfacial ultrastructure and microtensile dentin bond strength after five-year water storage. Oper Dent 2004; 29(6): 705-12.
19. Armstrong SR, Vargas MA, Fang Q, Laffoon JE. Microtensile bond strength of a total-etch 3-step, total-etch 2-step, self-etch 2-step, and a self-etch 1-step dentin bonding system through 15-month water storage. J Adhes Dent 2003; 5(1): 47-56.
20. Van Landuyt KL, Snauwaert J, De Munck J, et al. Systematic review of the chemical composition of contemporary dental adhesives. Biomaterials 2007; 28(26): 3757-85.
21. Ferracane JL. Hygroscopic and hydrolytic effects in dental polymer networks. Dent Mater 2006; 22(3): 211-22.
22. Jaffer F, Finer Y, Santerre JP. Interactions between resin monomers and commercial composite resins with human saliva derived esterases. Biomaterials 2002; 23(7): 1707-19.
23. Bourbia M, Ma D, Cvitkovitch DG, Santerre JP, Finer Y. Cariogenic bacteria degrade dental resin composites and adhesives. J Dent Res 2013; 92(11): 989-94.
24. Gregson KS, Jack Windsor L, Platt JA. Biodegradation of a dental resin material by fibroblast conditioned media. Dent Mater 2009; 25(11): 1358-62.
25. Finer Y, Santerre JP. Salivary esterase activity and its association with the biodegradation of dental composites. J Dent Res 2004; 83(1): 22-6.
26. Finer Y, Santerre JP. Biodegradation of a dental composite by esterases: dependence on enzyme concentration and specificity. J Biomater Sci Polym Ed 2003; 14(8): 837-49.
27. Shokati B, Tam LE, Santerre JP, Finer Y. Effect of salivary esterase on the integrity and fracture toughness of the dentin-resin interface. J Biomed Mater Res B Appl Biomater 2010; 94(1): 230-7.
28. Kermanshahi S, Santerre JP, Cvitkovitch DG, Finer Y. Biodegradation of resin-dentin interfaces increases bacterial microleakage. J Dent Res 2010; 89(9): 996-1001.
29. Sadeghinejad L, Cvitkovitch DG, Siqueira WL, Merritt J, Santerre JP, Finer Y. Mechanistic, genomic and proteomic study on the effects of BisGMA-derived biodegradation product on cariogenic bacteria. Dent Mater 2017; 33(2): 175-90.
30. Singh J, Khalichi P, Cvitkovitch DG, Santerre JP. Composite resin degradation products from BisGMA monomer modulate the expression of genes associated with biofilm formation and other virulence factors in Streptococcus mutans. J Biomed Mater Res A 2009; 88(2): 551-60.
31. Birkedal-Hansen H, Moore WG, Bodden MK, et al. Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 1993; 4(2): 197-250.
32. Jain A, Bahuguna R. Role of matrix metalloproteinases in dental caries, pulp and periapical inflammation: An overview. J Oral Biol Craniofac Res 2015; 5(3): 212-8.

33. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 2003; 92(8): 827-39.
34. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 2006; 69(3): 562-73.
35. Tallant C, Marrero A, Gomis-Ruth FX. Matrix metalloproteinases: fold and function of their catalytic domains. Biochim Biophys Acta 2010; 1803(1): 20-8.
36. Sorsa T, Tjaderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis 2004; 10(6): 311-8.
37. Palosaari H, Ding Y, Larmas M, et al. Regulation and interactions of MT1-MMP and MMP-20 in human odontoblasts and pulp tissue in vitro. J Dent Res 2002; 81(5): 354-9.
38. Martin-De Las Heras S, Valenzuela A, Overall CM. The matrix metalloproteinase gelatinase A in human dentine. Arch Oral Biol 2000; 45(9): 757-65.
39. Mazzoni A, Papa V, Nato F, et al. Immunohistochemical and biochemical assay of MMP-3 in human dentine. J Dent 2011; 39(3): 231-7.
40. Mazzoni A, Nascimento FD, Carrilho M, et al. MMP activity in the hybrid layer detected with in situ zymography. J Dent Res 2012; 91(5): 467-72.
41. van Strijp AJ, Jansen DC, DeGroot J, ten Cate JM, Everts V. Host-derived proteinases and degradation of dentine collagen in situ. Caries Res 2003; 37(1): 58-65.
42. Wang DY, Zhang L, Fan J, et al. Matrix metalloproteinases in human sclerotic dentine of attrited molars. Arch Oral Biol 2012; 57(10): 1307-12.
43. Llano E, Pendas AM, Knauper V, et al. Identification and structural and functional characterization of human enamelysin (MMP-20). Biochemistry 1997; 36(49): 15101-8.
44. Mazzoni A, Scaffa P, Carrilho M, et al. Effects of etch-and-rinse and self-etch adhesives on dentin MMP-2 and MMP-9. J Dent Res 2013; 92(1): 82-6.
45. Montagner AF, Sarkis-Onofre R, Pereira-Cenci T, Cenci MS. MMP Inhibitors on Dentin Stability: A Systematic Review and Meta-analysis. J Dent Res 2014; 93(8): 733-43.
46. Breschi L, Martin P, Mazzoni A, et al. Use of a specific MMP-inhibitor (galardin) for preservation of hybrid layer. Dent Mater 2010; 26(6): 571-8.
47. Perdigao J, Reis A, Loguercio AD. Dentin adhesion and MMPs: a comprehensive review. J Esthet Restor Dent 2013; 25(4): 219-41.
48. Tezvergil-Mutluay A, Mutluay M, Seseogullari-Dirihan R, et al. Effect of phosphoric acid on the degradation of human dentin matrix. J Dent Res 2013; 92(1): 87-91.
49. Ozcan S, Seseogullari-Dirihan R, Uctasli M, Tay FR, Pashley DH, Tezvergil-Mutluay A. Effect of polyacrylic acid on dentin protease activities. Dent Mater 2015; 31(8): 901-6.
50. Mazzoni A, Apolonio FM, Saboia VP, et al. Carbodiimide inactivation of MMPs and effect on dentin bonding. J Dent Res 2014; 93(3): 263-8.
51. Palasuk J, Windsor LJ, Platt JA, Lvov Y, Geraldeli S, Bottino MC. Doxycycline-loaded nanotube-modified adhesives inhibit MMP in a dose-dependent fashion. Clin Oral Investig 2018; 22(3): 1243-52.
52. Tjaderhane L, Buzalaf MA, Carrilho M, Chaussain C. Matrix metalloproteinases and other matrix proteinases in relation to cariology: the era of 'dentin degradomics'. Caries Res 2015; 49(3): 193-208.
53. Song F, Wisithphrom K, Zhou J, Windsor LJ. Matrix metalloproteinase dependent and independent collagen degradation. Front Biosci 2006; 11: 3100-20.
54. Tersariol IL, Geraldeli S, Minciotti CL, et al. Cysteine cathepsins in human dentin-pulp complex. J Endod 2010; 36(3): 475-81.
55. Abu Nawareg M, Elkassas D, Zidan A, et al. Is chlorhexidine-methacrylate as effective as chlorhexidine digluconate in preserving resin dentin interfaces? J Dent 2016; 45: 7-13.
56. Yiu CK, Hiraishi N, Tay FR, King NM. Effect of chlorhexidine incorporation into dental adhesive resin on durability of resin-dentin bond. J Adhes Dent 2012; 14(4): 355-62.
57. Sartori N, Stolf SC, Silva SB, Lopes GC, Carrilho M. Influence of chlorhexidine digluconate on the clinical performance of adhesive restorations: a 3-year follow-up. J Dent 2013; 41(12): 1188-95.
58. Araujo MS, Souza LC, Apolonio FM, et al. Two-year clinical evaluation of chlorhexidine incorporation in two-step self-etch adhesive. J Dent 2015; 43(1): 140-8.
59. Montagner AF, Perroni AP, Correa MB, Masotti AS, Pereira-Cenci T, Cenci MS. Effect of pre-treatment with chlorhexidine on the retention of restorations: a randomized controlled trial. Braz Dent J 2015; 26(3): 234-41.
60. Loguercio AD, Stanislawczuk R, Malaquias P, Gutierrez MF, Bauer J, Reis A. Effect of Minocycline on the Durability of Dentin Bonding Produced with Etch-and-Rinse Adhesives. Oper Dent 2016; 41(5): 511-19.
61. Balalaie A, Rezvani MB, Mohammadi Basir M. Dual function of proanthocyanidins as both MMP inhibitor and crosslinker in dentin biomodification: A literature review. Dent Mater J 2018; 37(2): 173-82.
62. Liu Y, Chen M, Yao X, Xu C, Zhang Y, Wang Y. Enhancement in dentin collagen's biological stability after proanthocyanidins treatment in clinically relevant time periods. Dent Mater 2013; 29(4): 485-92.
63. Liu Y, Dusevich V, Wang Y. Proanthocyanidins rapidly stabilize the demineralized dentin layer. J Dent Res 2013; 92(8): 746-52.
64. Tezvergil-Mutluay A, Agee KA, Uchiyama T, et al. The inhibitory effects of quaternary ammonium methacrylates on soluble and matrix-bound MMPs. J Dent Res 2011; 90(4): 535-40.