COMPOSITE RESINS: A REVIEW OF ADHESIVE FAILURE FROM ENZYMATIC DEGRADATION

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ABSTRACT

Aim: This study aims to review the concepts and metalloproteinase activation mechanisms and cathepsin cysteine.

Material and Methods: The literature review was conducted around the main keywords “cathepsin cysteine", "metalloproteinases", "dentin-adhesive interface” and “degradation”.

Results: Nineteen articles were collected and included only articles available in its entirety, on english.

Conclusions: Many studies are still being conducted incorporating different substances that help by inhibiting the action of these enzymes, however, there is still no consensus on the best element to be used in restorative procedures.

KEYWORDS: metalloproteinases, cathepsin cysteine, adhesive interface, restorative procedures

INTRODUCTION

Traditional methods mechanical retention of restorative materials have been replaced by current concepts of conservative restorative dentistry[1]. Thus, the adhesive techniques have been developed and are often revised seeking to achieve excellence in the procedure.

The adherence phenomenon is defined as the state in which two surfaces of different molecular composition are joined according to attraction forces[2].

In the hybridized dentin, the mechanical bond by theentrapment of polymers in collagen fibers. The chemical adhesion is influenced by the wetting ability of the adhesive, which is evidenced by the degree of contact between the surfaces. However, dentin contains a large percentage of water and organic material and because of its dynamic nature, over the years, there is the occurrence, the marginal infiltration of restoration, caused by the degradation of the collagen matrix of which has not been fully infiltrated by adhesive system[3-7]. This degradation can still occur through activation of metalloproteinases and cysteine cathepsins, which after acid etching becomes free to perform its enzymatic action, since removes minerals protective dentinal tissue.

In order to control this degradative action, there are several studies involving mechanisms of inhibition of these enzymes such as Chlorhexidine solution and the natural inhibitor called *Epigallocatechin gallate* (EGCg)[8-9].

This study aims to review the concepts and metalloproteinase activation mechanisms and cathepsin cysteine, as well as the study of inhibition of them through the current application

of chlorhexidine solution, EGCg and other substances for improvement in longevity of dental technique.

MATERIAL AND METHODS

The literature review was conducted in the Science Direct, SCIELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Health Sciences) and MEDLINE (National Library of Medicine, USA) databases.

It was used as descriptors the terms "cathepsin cysteine", "metalloproteinases", "dentin-adhesive interface", "degradation", in the period of five years.

It was found 19 articles that contained important contributions on the topic adherence and its mechanisms, as well as the degradation of adhesive interface through metalloproteinase and cathepsin cysteine (Table 1).

RESULTS

Several relevant PubMed indexed articles from 1999 to 2013 were electronically searched by typing "dosimeters", "dosimeters in dentistry", "properties of dosimeters", "thermoluminescent and optically stimulated dosimeters", "recent advancements in dosimetry in dentistry." The searches were limited to articles in English to prepare a concise review on dental dosimetry. Titles and abstracts were screened, and articles that fulfilled the criteria of use of dosimeters in dental applications were selected for a full-text reading.

Literature was reviewed under following groups: (1) properties of dosimeters, (2) types of dosimeters, (3) recent advancements in dental dosimetry, (4) results of studies using different dosimeter in dentistry.

DISCUSSION

Many studies have reported the degradation of the organic components of the hybrid layer, thus, studies have been developed in order to understand the role of intrinsic enzyme content of dentin organic matrix. They identified the existence of several matrix metalloproteinases (MMPs) and cysteine cathepsins dentin. It is suggested that these, when activated, are responsible for the collagen fibrils exposed degradation in adhesive interface[22].

In mineralized dentin, there is no penetration of adhesive, therefore, proceed to the acid etching, where the minerals are replaced by water wash after conditioning or the solvent used in acidified monomers. However, the depth of demineralization of dentin resulting from the application acids, generally exceeds the infiltration capacity of the resin monomers, resulting in formation of a zone lacking of demineralized dentin protection. This inability to completely cover this exposed collagen matrix occurs both for conventional adhesives as to self-etch[15],thus, that failure plus to the dynamic flux of water let the surface vulnerable to a hydrolytic degradation, resulting in adhesive failures.

Since most restorative procedures are performed in decayed teeth, it is necessary, therefore, that the reviewed studies should be carried out in these conditions. In carious dentin is an increase of porosity and lower mineral content observed in the intertubular dentine affected thereby diffusion of the agent acid is larger[23-27]. Thus, a hybrid layer filled with imperfections and more susceptible to degradation of the adhesive interface is built[25-26].The adhesive interface degradation mechanisms involve the deterioration of both polymeric constituents as the collagen fibrils devoid of protection.

The studies are currently conducted in the enzymatic activity as the main cause of degradation of the hybrid layer. The main enzymes are the matrix metalloproteinases (MMPs) and cysteine cathepsins. The first feature is being zinc and calcium dependent and are able to degrade almost all extracellular matrix components. In human there are more than 23 types of metalloproteinases, subdivided into 6 families: collagenases, gelatinases, stromelysins, matrilysins, membrane type MMPs and other MMPs (based on substrate specificity)[14,28]. The MMPs are initially synthesized as inactive pro-enzymes, referred to as zymogens, and the likely activation mechanism involves the changes of pH and others enzymes[14,29].In addition to the degradative action, MMPs are involved in enamel formation and fluorosis, and are also identified in inflammatory processes in the pulp and periapical region in periodontal diseases[17,19]

The cathepsins cysteines are lysosomal enzymes, there is 11 differents types. As these MMPs are synthesized as zymogens and then transported to endosomes. Its activation is riggered mainly by acidification of pH, but may also be linked to other proteases[7,15].

Numerous studies of enzyme activation mechanism are currently being performed and a hypothesis to be clarified is the possibility of synergism between the two classes of proteolytic enzymes[17,19]. However, the identification of several cathepsins in dentin can elucidate the potential cathepsin-MMP interactions collagen degradation also in the hybrid layer[17].

Table 1. Studies research about metalloproteinases and cathepsin cystein.

Author	Objectives	Inhibition proteases	Conclusion
Golub et al., 1998[10]	Studying the inhibit ability of metalloproteinases by tetracyclines	Doxycycline	A sub-antimicrobial dose of doxycycline can suppress collagenase activity
Gendron et al., 1999[9]	Evaluating the inhibitory effect of different chlorexidine concentrations on the activities of MMP-2, -8, and -9, in the treatment of periodontitis	Chlorexidine concentrations on 0.03, 0.015, 0.008, 0.004, 0.002, and 0.0001%	The minimal concentration of CHX that led to a complete inhibition of MMP-9 activity was 0.002%, whereas MMP-2 activity was 0.0001%
Perdigão et al., 1999[1]	Review article to summarize the most recent concepts in dentin bonding	-	Clinical and laboratory studies lack information on the dynamic behavior of the substrate in a vital environment
Demeule et al., 2000[11]	Investigating the effects of different biologically active components from natural products on matrix metalloproteinase activities	Green tea polyphenols (GTP), resveratrol, genistein and organosulfur compounds from garlic.	The catechins from green tea inhibited the MMP activities
Pashley et al., 2004[5]	Determining if acid-etched dentin matrices can be degraded by dentin-derived proteolytic enzymes, in the absence of bacterial colonization	The proteases inhibitos as benzamidine HCl (2.5), ε-amino-*n*-caproic acid (50), N-ethylmaleimide (0.5), phenylmethylsufonyl fluoride (0.3) and chlorexidine (0.2)	Low levels of collagenolytic activity that was inhibited by protease inhibitors or 0.2% chlorhexidine
Hebling et al., 2005[12]	Verify if there are differences between the degradation of dentin bonded with an etch-and-rinse adhesive and that with chlorhexidine	CHX	The use of chlorhexidine as an MMP inhibitor resulted in the arrest of the in vivo degradation of the hybrid layers
Chaussain-Miller et al., 2006[8]	A review to summarize the understanding of the role of host matrix metalloproteinases in the caries process	-	MMP inhibition by several inhibitors, as natural substances, could provide a potential therapeutic pathway to limit caries progression in dentin
Carrilho et al., 2007[13]	Verify if interfacial degradation of resin-dentin bonds may be prevented or delayed by the application of CHX	CHX	Auto-degradation of collagen matrices can occur in resin-infiltrated dentin, but may be prevented by chlorhexidine
Hannas et al., 2007[14]	A review focusing on metalloproteinases and their role in physiological and pathological extracellular matrix	-	The use of MMP inhibitors could help the prevention and treatment of many MMP-related oral diseases
Zhang et al., 2009[15]	Summarizing the knowledge of the role of dentinal hostderived MMPs in the reduction of dentin bonding	-	New bonding systems should provide durable MMP-inhibitory functionality to preserve the integrity of the hybrid layer and to improve dentin bonding durability of adhesive restorations
Kato et al., 2010[16]	Testing the hypothesis that gels containing MMP inhibitors can prevent dental erosion	EGCg and CHX	The use of gels delivering MMP inhibitors was shown to prevent erosion
Tersariol et al., 2010[6]	Hypothesized that odontoblasts express other collagen-degrading enzymes such as cysteine cathepsins in dentin	-	It was found that presence of cysteine cathepsins in dentin and suggest their role, along with MMPs, in dentin modification
Liu et al., 2011[3]	Review article about dentin bonding and the experimental strategies available to prevent degradation of resin-dentin bonds	-	A combination of 5 strategies result in overcoming the critical barriers to progress currently encountered indentin bonding
Scaffa et al., 2012[17]	Investigating whether CHX could inhibit cysteine cathepsins present in dentin	CHX	CHX is a potent inhibitor of the cysteine cathepsins-proteolytic enzymes present in the dentin-pulp complex
Tjäderhane et al., 2013[7]	A review to identity the function of the collagen-degrading proteolytic enzymes in dentin	-	Matrix metalloproteinases and cysteine cathepsins in mineralized dentin and dentinal fluid contribute to enzymatic degradation of the composite adhesive hybrid layer collagenous matrix

Author	Objectives	Inhibition proteases	Conclusion
Epasinghe et al., 2013[18]	Evaluating the inhibitory effect of a natural collagen cross-linker, on soluble and matrix-bound proteases	Proanthocyanidin	Proanthocyanidin presented both dentine MMP and cysteine cathepsins inhibition, which was higher than chlorhexidine
Zarella 2013[19]	Evaluating the ability of experimental resins containing known matrix protease inhibitors on the inhibition of gelatinases and collagenases	EGCg and CHX	The EGCg and CHX was able to reduce the MMP-2 and -9 activities
Scheffel et al., 2015[20]	Evaluating the effect of carbodiimide treatments of acid-etched dentin on resin-dentin bond strength	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)	0.5 mol/L EDC as able to prevent resin-dentin bond degradation after 12 months
Frasseto et al., 2016[21]	A review to investigate the processes responsible for degradation of resin-bonded interfaces and the approaches to prevent it	-	Inhibition of the collagenolytic activity and the use of cross-linking agents are the main strategies to increase the resistance of the hybrid layer

Many synthetic elements have been studied to act as non-specific inhibitors of MMPs and cathepsins cysteines. Chlorhexidine has been used more recently as an inhibitor of MMPs, the concentration of 2% before the adhesive system application[12-13]. Pashley et al.[5] presented evidence of effectiveness in inhibiting collagenolytic enzymes. It is believed that the mechanism of action of this substance either by chelation of calcium, which is essential for the catalytic activity of the collagenase. There are few research with self-etching adhesive, and the results have been conflicting, however, the comparison between studies is not feasible because different tests are used, such as shear and microtensile.

The *Epigallocatechin gallate* (EGCg), has been widely studied.This substance is a polyphenol and is presented as active ingredient of green tea. Studies have demonstrated that there is a potent inhibitory activity of a substance known as MT1, which has the ability to activate the precursor form of an MMP.It is recognized that the mechanism of inhibition is related to the fact that EGCg appears to link to the collagenase by hydrogen bonds and hydrophobic interactions cause conformational changes in order to mask the catalytic site. It is appropriate to emphasize that this is a natural product that has no side effects.It is described that the minimum inhibitory concentration of the substance to inhibit MMP-2 and MMP-9 is 0.00075% and therefore lower than chlorhexidine[9,11,19,30].

The ethylenediamine tetraacetic acid (EDTA) has been studied because it is an organic compound which acts as a chelating agent, forming very stable complexes with various ions such as calcium. The chelation with calcium save the mechanical properties of the dentin, since MMPs are dependent on this chemical element. However, studies have indicated that the EDTA washing after demineralization, leads to a significant reduction of the properties of demineralized dentin, being accompanied by degradation of collagen, indicating that MMP inhibition would be reversible[15,17].

Recent studies showed that it is possible to incorporate substances on restorative materials and adhesives[19].The amount of these substances could influence the material properties. If found the possibility of inclusion of these substances in composite resin, would be an excellent substitute for dentin in restorative procedures, increasing the longevity of the material for the preservation of the hybrid layer. However it is suggested that the incorporation of chlorhexidine resins can be difficult to polymerization process and result in a higher level of residual monomers, leading to inferior mechanical properties[31-32]. Thus, others studies was performed to incorporate Therefore, further studies were conducted with the incorporation of substances primers. The compound used currently is called EDC (1-ethyl-3-3-dimethylaminopropyl) carbodiimide[20]. This is a cross linker, which promote collagen crosslinking in protecting the site of activation of enzymes. However, after application, it is removed from the dentin surface, reacting with proteins available only for the period of contact between the solution and the dentin. The incorporation of the EDC primer adhesive system could achieve the same effect on collagen and MMPs, and remains in the adhesive interface and be released slowly giving

somewhat hybrid layer to the ability to self-preserve[20].

CONCLUSIONS

Metalloproteinases and cathepsins contribute to enzymatic degradation process of the hybrid layer. Currently, many studies are still being conducted incorporating different substances that help by inhibiting the action of these enzymes, however, there is still no consensus on the best element to be used in restorative procedures. It is suggested that further studies be carried out with affected dentin caries.

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