Activity of Matrix Metalloproteinases (Mmps) Production by Dentine Matrix Depending on The Used Adhesive System: A Systematic Review.

Zurab Khabadze[1], Irina Makeeva[1], Mariya Makeeva[1], Ahmad Wehbe[1], Ekaterina Shilyaeva[1], Khadizhat Omarova[1], Anastasiia Ivina[1], Yunus Bakaev[1], Fikret Badalov[1], Emma Demurova[1], Ivan Gorbatenko[2], Oleg Mordanov[1]

1. RUDN University, Moscow, Russia.
2. Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia.

Abstract

Matrix metalloproteinases (MMPs) are a group of enzymes that are correlated with the degradation of the hybrid layer. This article describes the effect of adhesive systems on the MMPs.

A systematic review of the literature was conducted analyzing articles published on PubMed, Google scholar, Scopus, ResearchGate and ScienceDirect between 2011 and 2021, activity of the MMPs was the selected outcome variable. A total of 22 publications were selected, 9 of which were selected for detailed review. Chief question in this article was: which generation of adhesive systems has more effect on MMPs? How does it affect them?

Etch-and rinse adhesive systems showed higher level gelatinolytic activity, when compared to Self-etch adhesive systems.

Activation of the MMPs is due in most adhesive systems, which is responsible for the degradation of the hybrid layer. Etch-and-rinse adhesive systems showed higher gelatinolytic activity when compared to self-etch adhesive systems. further studies are needed on new chemicals capable of inhibiting MMP activity. Moreover, further studies are needed to check MMP activity in non-vital teeth.

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Introduction

Matrix metalloproteinases (MMPs) are enzymes of the endopeptidase family, that are part of the extracellular matrix, MMPs are calcium and zinc-dependent, of an endogenous origin, which are crucial for tooth development[1,2,3,4,5,6]. In mineralized dentin, MMPs are secreted to the extracellular matrix in non-functional proenzyme (zymogens) state as they are immobilized by apatite nanocrystals[2,3,7,8,9,10]. Recent studies have shown that the activation of MMPs is associated with the presence of an acidic environment, increase in temperature, the presence of growth factors, cytokines, physical stress, fillings/dentures containing mercury or gold[6,9,11]. In humans, MMPs are classified into 6 groups based on their putative substrate specificity and internal homologies – Collagenases, Gelatinases, Stromelysins, Matrilysins, membrane-type MMPs and other MMPs[11,12,13]. The MMPs of interest in this literature review are the Gelatinases: MMP-2 (Gelatinase A, 72kDa gelatinase) and MMP-9 (Gelatinase B, 93kDa Gelatinase)[14,15]. MMP-2, with a molecular weight of 72 kDa, in a physiological state is synthesized by macrophages, fibroblasts, dendritic cells, endothelial cells, hematopoietic cells and odontoblasts[13,15,16]. MMP-9 has a molecular weight of 93 kDa and is nearly absent in normal tissues as it is covered by neutrophils, macrophages, mast cells, fibroblasts, and lymphocytes[17,18].

One of the main goals in modern day restorative dentistry, is to create more durable adhesive-dentin interface, that would last in long term, providing retentive strength, marginal seal,

*Corresponding author:
Oleg Mordanov
RUDN University, Moscow, Russia.
E-mail: mordanov19@gmail.com

clinical durability and protect collagen fibrils of the dentin matrix from degeneration[15,16].

Adhesion to dentin depends on the formation of the hybrid layer, which is formed by infiltrating the resin monomer into the scaffolds of the demineralized dentin collagen matrix.[10,11]

Despite the advance in dental materials, the hybrid layer created on the dynamic and variable dentin is not perfect and may fail over time, including marginal leakages and discolorations and subsequent loss of retention of composite restoration[15]. Recent studies suggest that the degradation of the hybrid layer is due to the use of phosphoric acid as the etching agent in the bonding procedures which mobilizes and activates the MMPs, that are responsible for the digestion of collagen fibrils exposed at the adhesive interface[6,10,11,14]. Neves et al. suggested that the degradation of the hybrid layer can occur by a dual mechanism: alteration to the adhesive matrix\dentin matrix, due to contact with saliva and\or the presence of bacteria, the presence of bacterial microleakage decreases pH and activates degrading proteins[12].

In adhesive dentistry, adhesive systems are classified by generation, into 8 generations, based on the complexity of the bonding agents; the introduction of a new generation have made an effort to reduce the number of clinical steps, deliver quicker application techniques, and most importantly, to provide better chemistry to facilitate a stronger bond[21,22]. In modern day adhesive dentistry, 1st, 2nd, and 3rd generation have been rendered completely obsolete and substituted by more modern analogs[21]. Moreover, they can be classified by their interaction with the smear layer: Etch-and-rinse adhesive systems, which include the application of phosphoric acid on tooth structures in a two or three step protocol, which is then followed by a rinse that removes the smear layer; and Self Etch adhesive systems, that on the other hand, uses non-rinsing acidic primer, that integrates the smear layer residues into the adhesive interface in a one or two step protocol[21,22]. And there are the “Universal” adhesive systems that function in etch-and-rinse and self-etch modes[10,13,21,22].

The introduction of the 3-step etch-and-rinse 4th generation adhesive system, which was the first of its kind to achieve complete removal of the smear layer, still remains the “golden standard” until this day[21].

The goal of our literature review was to observe the production activity of the MMPs based on the used adhesive system, as different adhesive systems have different pHs, which is one of the factors that might affect the activation of the MMPs.

Materials and methods

Protocol

This review follows the PRISMA (Preferred Reporting Items for Systematic review and Meta-analysis. A detailed protocol following the PICO protocol was designed to answer the following question: which generation of adhesive systems has more effect on MMPs? How does it affect them? (P) Patient/Problem: hybrid layer degradation. (I) intervention: MMP inhibitors. (C) control: control samples from non-treated teeth. (O) Outcome: increase/decrease in activity of the MMPs.

Selection criteria

Publications that met the following criteria were included:

1. Full-text articles in English, not older than 10 years.
2. Articles containing relative information about the topic of research.
3. Studies conducted on human teeth.

Publications that had no relative data to the topic of study and literature reviews were dropped out.

Information sources

Electronic search of English literature was carried out in November 2021, in the databases of PubMed, Google scholar, Scopus, ResearchGate and ScienceDirect. The search started on the 10th of November 2021 and ended on the 21st of November 2021.

Search and selection of studies

The combination of these keywords was used in the search: activity of MMPs, production of MMPs, activation of MMPs, adhesives systems, MMPs production by adhesives, gelatinolytic/collagenolytic activity by adhesives, etch-and-rinse adhesive, self-etch adhesive. As a result, 22 articles from PubMed, Google scholar, Scopus, ResearchGate and ScienceDirect were analyzed.

Data collection process

Data was extracted from the studies in accordance with the interest of the current review.

Inclusion and exclusion criteria

The literature search was limited to publications published in the English language. The inclusion criteria were studies containing information about enzyme activity in human teeth; the period in which they are active, after the application of the adhesive system, from randomized, non-randomized clinical studies, and clinical research. Studies with irrelevant information were excluded.

Outcome variables

The following 2 outcome variables were defined: A) MMPs activity, B) adhesive generation used.

Data extraction

All headlines were screened to drop out irrelevant results. Onwards, abstracts were screened to analyze the number of teeth and the main characteristics of the study. The publications that remained after the abstract screening were analyzed according to inclusion/exclusion criteria. At last, 9 articles were included in the present review.

Statistical analysis

A meta-analysis of the data reported in this systematic review could not be performed, due to the heterogeneity of the data of the manuscripts included.

Risk of bias.

Risk of Bias was not conducted.

Results

22 titles were obtained from the electronic search, ranging from 2011 to 2021. The first screening of headlines and abstracts led to the inclusion of 9 manuscripts.

All analysis were performed using *in situ* zymography according to the protocol employed by Mazzoni et al.[3-7,10,11,13], with the exception of Costa et al., that used Immunoxpression to determine the activity of MMP-9 overtime[9]. All researchers applied the adhesive system protocol according to the manufacturer's instructions.

Regarding the 9 included articles, all were clinical research. In the selected literature, a total number of 142 vital third molars were used.

A) MMPs activity: mainly due to the application of phosphoric acid onto tooth structures, the MMPs are activated after being in their immobile state, which in long term contributes in the degradation of collagen in the hybrid layer created by the adhesive system that is crucial to achieve durable dentin-adhesive interface. Different adhesive systems have variable pH levels, etch-and-rinse adhesive systems (4th and 5th generations) use phosphoric acid as an etching agent as the first step of the adhesive protocol that has a low acidic pH that ranges from 0.1 to 0.4; on the opposite side, self-etch adhesive systems (6th, 7th, and 8th generations) use non-rinsing acidic primer that has pH that ranges from 0.8 to 3.3 that contribute in the activation of the MMPs. All reviewed research demonstrated that etch-and-rinse adhesive systems showed higher enzymatic activity. Mazzoni et al. conducted a study that concluded that etch-and-rinse adhesive systems shower higher MMP activity, at 9-83% for MMP-2 and 24-74% for MMP-9; on the other hand, self-etch adhesive systems achieved 13-20% for MMP-2 and 23-48% for MMP-9[3].

B) Adhesive generation: many adhesive systems by various companies were used by the researchers. The use of 10% phosphoric acid with Optibond FL (Kerr, Orange, CA, USA) 4th generation adhesive system showed increased enzymatic activity of MMP-2 and MMP-9 [4,10]. 5th generation adhesive systems were heavily involved in this literature review, Adper Scotchbond 1XT (3M ESPE, St. Paul, MN, USA), PQ1 (Ultradent, Salt Lake City, UT, USA); Optibond Solo Plus (Kerr, Orange, CA, USA), Prime&Bond NT (Dentsply, Konstanz, Germany), Clearfil SE (Kuraray Medical Inc, Tokyo, Japan), XP Bond (Dentsply, Konstanz, Germany), Adper Single Bond (3M ESPE, St. Paul, MN, USA) were examined; Scotchbond 1XT (3M ESPE, St. Paul, MN, USA) showed the highest enzymatic activity of MMP-2, and Prime&Bond NT (Dentsply, Konstanz, Germany) had the highest enzymatic activity of MMP-9[3,4,7,9,11]. furthermore, Clearfil SE (Kuraray Medical Inc, Tokyo, Japan) showed a slight decrease of enzymatic activity of pro-MMP-9 and complete inactivation of MMP-2/pro-MMP-2 [5,9]. From the 7th generation adhesive systems, Adper Easy Bond (3M ESPE, St. Paul, MN, USA)

showed the highest MMP-2 enzymatic activity and Tri-S (Kuraray, Tokyo, Japan) had the highest MMP-9 enzymatic activity[3,6,14]. Universal adhesive systems as Scotchbond Universal Adhesive 3M ESPE (St. Paul, MN, USA) showed higher MMP-2/9 enzymatic activity in etch-and-rinse mode[10,13].

Discussion

From the analysis of the literature, not many studies concerning the MMPs enzymatic activity of different adhesive systems were published. No systematic reviews or meta-analysis were found in the literature. Thus, the purpose of this literature review was to evaluate the reported data in literature analyzing two main aspects: A) MMPs activity and B) adhesive generation.

The topic was focused on the enzymatic activity of MMPs while using different adhesive systems. Adhesive systems can be simply classified onto etch-and-rinse and self-etch adhesive systems, according to the literature, all studies showed that the use of etch-and-rinse adhesive systems contributed to a highest level gelatinolytic activity. Regarding MMPs activity, all research was analyzed using in situ zymography[3,4,5,6,7,10,11,13,23,24], with the exception of Costa et al. that utilized immunohistological staining using labeled streptavidinbiotin amplification system (LSAB - Dako, Glostrup, Denmark) and the monoclonal antibody anti-MMP-9 in his study, which concluded that the use of 37% phosphoric acid with XP Bond (Dentsply, Konstanz, Germany) showed intense activity of MMP-9 for 7 days which was predominant in the dentinal tubules and odontoblatic layer[9]. Furthermore, research conducted by Mahalaxmi et al. concluded that Adper Single Bond (3M ESPE, St. Paul, MN, USA) showed increased gelatinolytic activity for 7 days[11]. Other studies investigated MMPs inhibitors, such as chlorhexidine and 1-ethyl-3 (3-dimethylaminopropyl) carbodiimide (EDC). Chlorhexidine is a well-know and well-documented MMPs inhibitor, as it is capable of altering the three-dimensional structure of MMPs and chelating the zinc and calcium ions, which are necessary for the activation of the MMPs[2,4,8,14]. Chlorhexidine can inactivate dentinal MMPs in a low concentration such as 0.02%[1,2,8,14]. As stated by Tjäderhane et al. that the pre-treatment of acid-etched dentin with 0.02% Chlorhexidine prior to the adhesive application decreased MMPs detection level by 27% [14]. On the other hand, EDC is a non-specific cross linker protein with low toxicity, that inactivates the catalytic and cathepsin parts of MMPs by the activation of carboxylic groups and amino-acid cross-links. Studies showed that the application of EDC prior to the application of Optibond FL (Kerr, Orange, CA, USA), Adper Scotchbond 1XT (3M ESPE, St. Paul, MN, USA), and XP Bond (Dentsply, Konstanz, Germany) showed complete inactivation of gelatinases[2,4,14].

Conclusions

Activation of the MMPs is due in most adhesive systems, which is responsible for the degradation of the hybrid layer. Etch-and-rinse adhesive systems showed higher gelatinolytic activity when compared to self-etch adhesive systems. further studies are needed on new chemicals capable of inhibiting MMP activity. Moreover, further studies are needed to check MMP activity in non-vital teeth.

Declaration of Interest

The authors report no conflict of interest.

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