Quest Journals
Journal of Medical and Dental Science Research
Volume 11~ Issue 11 (2024) pp: 06-11
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

The Dual-edged Role of MMPs and MMP Inhibitors in Restorative Dentistry: Pros, Cons, and Clinical Implications: A Comprehensive Review

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Abstract
Matrix metalloproteinases (MMPs) and their inhibitors take on a multifaceted impact on restorative dentistry, influencing both the integrity of dental materials and the healing processes of dental tissues. This review explores the dual-edged nature of MMPs and MMP inhibitors, highlighting their beneficial effects in promoting dental adhesion in restorative materials and compromised bond strength. We discuss the clinical implications of manipulating MMP activity, evaluating strategies for optimizing their roles in restorative procedures. This article reviews the role of MMPs in the breakdown of collagen within dentin and enamel, highlighting their contribution to dental caries and post-restorative failures. We discuss various MMP inhibitors, including synthetic compounds and natural agents, and their potential applications in enhancing the longevity and efficacy of dental restorations. The synergistic effects of these inhibitors with modern adhesive systems are explored, demonstrating their ability to improve bond strength and resistance to hydrolytic degradation. By integrating recent studies, research and clinical findings, this paper seeks to offer an in-depth insight into MMPs and their treypes of inhibitors can be effectively leveraged in restorative dentistry, while also addressing the challenges they pose to long-term treatment outcomes. Ultimately, our findings underscore the necessity for careful consideration of MMP dynamics to enhance both material performance and patient care in dental practice.

Keywords: *Matrix metalloproteinases (MMPs), MMP Inhibitors, Dental adhesion,Restorative dentistry*

***R**eceived 09 Nov., 2024; **R**evised 19 Nov., 2024; **A**ccepted 21 Nov., 2024 © The author(s) 2024.*
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I. INTRODUCTION

Matrix metalloproteinases (MMPs) appear to have a dual role in dentistry. While certain MMPs are crucial in the development of dental defects and caries, others seem to serve a protective function [1,2,3]. Collagen, the primary organic component of tooth structure, is degraded down by MMPs, while in the progression of dental caries. MMPs contribute in Extracellular matrix Degradation, involvement in tooth development, progression of dentin caries, and breakdown of the hybrid layer in resin–dentin bonded restorations.[3,4]. Matrix metalloproteinases (MMPs) Are essential enzymes implicated in the breakdown of the extracellular matrix components, including collagen, which is crucial for the durability and integrity of dental restorations [5,6]. This review examines the role of MMPs in collagen cleavage, the impact of their inhibition on the longevity of dental restorations, and current strategies to mitigate collagen degradation in clinical practice. MMPs play a significant role formation of dentin matrix [7,8], regulating the progression of caries, formation of secondary dentin and remodulation of tissues during various physiological processes, such as embryogenesis, morphogenesis, angiogenesis, and wound repair [9]. Additionally, MMPs are active in pulpitis and have been identified as potential

diagnostic markers for pulpal inflammation [10]. This review examines the pros and cons of MMPs in restorative dentistry

II. MMPS AND THEIR ROLE IN DENTISTRY

Matrix metalloproteinases (MMPs) are a group of enzymes that are essential for the breakdown and remodelling of components of the extracellular matrix, including collagen fibres, elastin, and glycoproteins[11], such as remodulation of tissues, wound healing, and development[12]. MMPs are also implicated in pathological conditions, including inflammation, cancer, and degenerative diseases, due to their ability to break down structural proteins in tissues[13,14]. In the context of dentistry, MMPs can aid in the breakdown of the dentin matrix, affecting the performance of dental adhesives and the durability of restorations[15].

Understanding MMPs and Their Role in Collagen Degradation

Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that break down extracellular matrix proteins [16,17]. In the context of dental restorations, MMPs such as MMP-2, MMP-8, and MMP-9 play a key role in the degradation of collagen fibers in dentin and adjacent tissues. This breakdown can compromise the effectiveness of bonding agents and the durability of restorative materials [5].

Several types of matrix metalloproteinases (MMPs) are of particular interest due to their roles in dentin bonding and degradation. The most commonly studied MMPs in this context include:

1. **MMP-2 (Gelatinase A)**: Involved in the degradation of type IV and type V collagen, MMP-2 plays a role in the breakdown of the dentin matrix.
2. **MMP-8 (Collagenase)**: Recognized for its role in the breakdown of type I collagen, MMP-8 is frequently associated with periodontal diseases and can affect the bonding interface in dental restorations.
3. **MMP-9 (Gelatinase B)**: Comparable to MMP-2, MMP-9 degrades type IV and type V collagen. It is also involved in inflammatory processes and tissue remodelling.
4. **MMP-20 (Enamelysin)**: While primarily associated with enamel formation, MMP-20's activity can impact dentin integrity and bonding effectiveness.
5. **MMP-14 (MT1-MMP)**: This membrane-type MMP is engaged in the activation of pro-MMPs and contributes to the remodelling of the extracellular matrix.

Impact of MMPs on Dental Restorations The stability of dental restorations relies heavily on the integrity of the collagen matrix[16]. MMPs, activated by various factors including bacterial infection and oxidative stress, can lead to the hydrolysis of collagen, resulting in reduced bond strength and premature failure of restorative materials[17,18]. This section reviews studies linking MMP activity with restoration longevity and performance. Strategies for MMP Inhibition Several approaches have been developed to inhibit MMP activity and improve the performance of dental restorations.[11]MMP Inhibitors Specific inhibitors targeting MMPs, such as doxycycline and batimastat, have shown promise in reducing collagen degradation. These inhibitors can be incorporated into dental materials or applied directly to tooth structures to prevent MMP-mediated damage[13]. Chemical Modifications Incorporating MMP inhibitors into adhesive systems and restorative materials can enhance their resistance to enzymatic breakdown. Research is ongoing into optimizing these chemical modifications for better clinical outcomes. Protective Agents Natural or synthetic compounds that exhibit MMP inhibitory properties can be used to protect the collagen matrix[8,10]. For example, chlorhexidine has been employed as a dual-purpose agent, providing both antimicrobial and MMP-inhibitory effects.

Clinical Implications and Future Directions The use of MMP inhibitors in clinical practice has the potential to significantly extend the lifespan of dental restorations. However, challenges remain in ensuring the effective and consistent application of these inhibitors[15,17]. Future research should focus on improving the delivery methods of MMP inhibitors, understanding their long-term effects, and integrating these strategies into routine dental procedures.

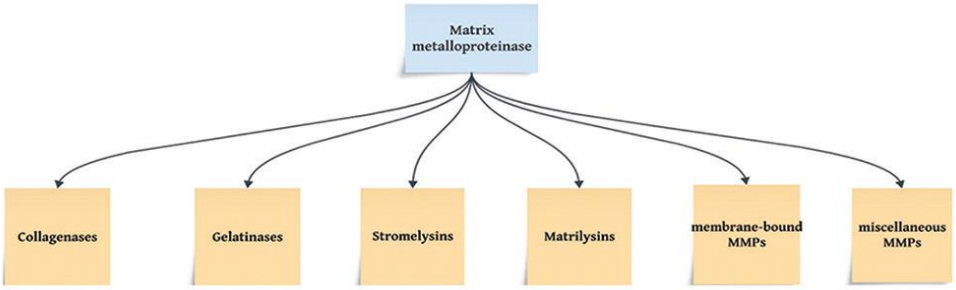

Figure 1: Classification of matri metalloproteinases - the six major groups [2]

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Inhibiting MMPs represents a promising strategy to prevent collagen degradation and enhance the longevity of dental restoration[7,12]. By addressing the enzymatic breakdown of collagen, dental professionals can improve the durability and performance of restorative materials. Continued research and clinical trials will be essential for refining these methods and determining best practices for their application in dental care.

III. EVIDENCE OF MMPS IN DENTIN:

Dentin is a mineralized tissue primarily composed of collagen, with inorganic apatite crystals embedded in an extracellular matrix (ECM). The ECM is mostly made up of Type I collagen, which accounts for about 90% of its organic content, while non-collagenous proteins, including proteoglycans, phospholipids, and enzymes, make up the remaining 10%. Among these enzymes, matrix metalloproteinases (MMPs) are particularly notable due to their role in various physiological and pathological processes within dentin. MMPs are zinc- and calcium-dependent enzymes capable of degrading almost all ECM components. The human MMP family consists of 23 members, classified into six groups based on substrate specificity. MMPs have a pro-domain, a catalytic domain, and other structural domains that influence their activity. They are produced by various cell types, including fibroblasts and epithelial cells. Nakabayashi, who introduced the concept of the hybrid layer, emphasized that dentinal peptides, especially collagen, should not be denatured during demineralization, as excessive acid exposure can expose underlying collagen and create a zone of weak dentin prone to degradation. This underscores the importance of preventing collagen degradation to maintain durable bond strength.

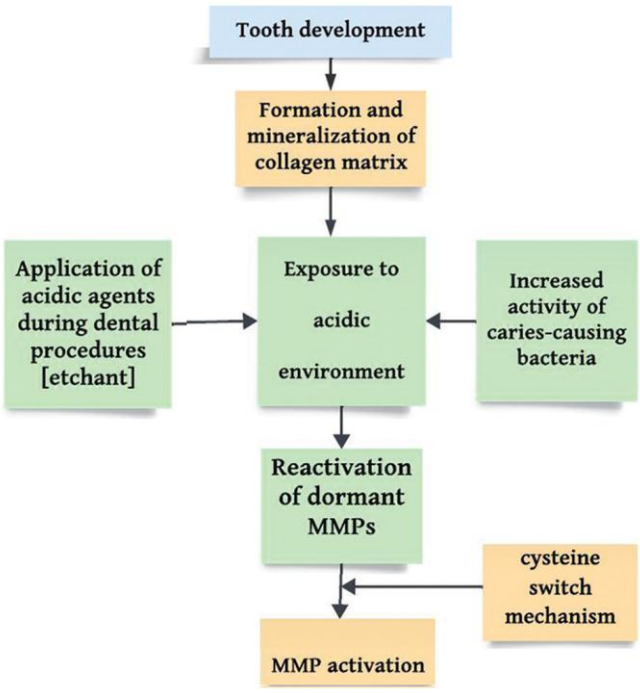

Figure 2: Mechanism of matrix metalloproteinase activation in human teeth**.** [2]

Mechanism of matrix metalloproteinase activation in human teeth:

- MMPs are secreted as inactive proenzymes (pro-MMPs).
- Activation occurs through proteolytic cleavage, changes in pH, or mechanical stresses.
- Metal ions (calcium, zinc) are essential for the catalytic activity of MMPs.
- Activated MMPs degrade ECM components, particularly collagen, affecting tooth integrity.
- Inflammatory mediators or dental treatments can exacerbate MMP activation.

- The activity of MMPs is regulated by inhibitors like TIMPs to maintain a balance between tissue remodelling and degradation.

IV. MMP INHIBITORS AND THEIR ROLE IN DENTISTRY:

MMP inhibitors in dental bonding help prevent the degradation of the hybrid layer, which is crucial for bond stability. By inhibiting matrix metalloproteinases (MMPs), these compounds reduce collagen breakdown, enhancing the longevity and strength of the bond between the tooth structure and restorative materials[6,7,8,9]. MMP inhibitors are particularly relevant for adhesive systems that rely on bonding to dentin. Dentin, which is a collagen-rich tissue, is prone to degradation over time due to the activity of MMPs, enzymes that break down collagen fibers[12,14]. When the hybrid layer (formed during the bonding process between the adhesive resin and the dentin) is degraded by MMPs, the bond can weaken, leading to premature failure of restorations.

Roles of MMP Inhibitors in Dental Bonding:

Preserving the Hybrid Layer: The hybrid layer is formed when resin infiltrates the demineralized dentin, creating a strong interface with the collagen fibers with the restorative material. MMPs naturally degrade collagen over time, especially when exposed to moisture and acidic conditions. MMP inhibitors prevent this enzymatic breakdown, helping maintain the integrity of the hybrid layer for a longer period[3,6,7].

Improving Bond Durability: Inhibition of MMPs helps maintain the strength of the bond between the adhesive and the dentin. Over time, MMP activity can cause the adhesive interface to degrade, reducing the bond's ability to withstand chewing forces, leading to bond failure or gaps[5,14,15].

Reducing Microleakage: MMPs, through their breakdown of collagen, can lead to gaps at the tooth-restoration interface, which can promote microleakage[11,16,18]. Microleakage allows bacteria and fluids to penetrate the bond interface, potentially leading to sensitivity, staining, or decay. MMP inhibitors can help minimize this risk by maintaining a stable bond.

Enhancing Resin Penetration: MMP inhibitors may also enhance resin infiltration into the dentin by preventing the degradation of the collagen matrix, thereby making it more accessible for the adhesive to penetrate and bond effectively.

V. CHLORHEXIDINE AS MMP INHIBITOR:

Chlorhexidine is a well-known antiseptic that has gained attention in restorative dentistry for its role as a matrix metalloproteinase (MMP) inhibitor. Chlorhexidine is effective in inhibiting various MMPs, especially MMP-2 and MMP-9, which play a role in the breakdown of collagen in dentin. By inhibiting these enzymes, chlorhexidine helps to preserve the structural integrity of the dentin matrix. The binding of chlorhexidine to dentin not only prevents MMP activity but also stabilizes the collagen structure, enhancing the longevity of the adhesive bond in restorative procedures. When used in dental adhesive systems, chlorhexidine can improve bond strength by preventing the degradation of the collagen matrix that occurs due to MMP activity, particularly in a moist environment [11,12,13 14]. Chlorhexidine is often used as an irrigant in endodontics, providing antimicrobial effects while also helping to preserve the integrity of dentin by inhibiting MMPs. Chlorhexidine's dual role as an antimicrobial agent and MMP inhibitor makes it particularly valuable in dental applications, addressing both infection control and structural preservation. The bond between CHX and dentinal surfaces forms through electrostatic interactions. Distilled water or artificial saliva is the recommended solution for aging [10]. The addition of 2% chlorhexidine (CHX) to acid-etched dentin or the phosphoric acid conditioner helps reduce collagen degradation [4,28], thereby enhancing immediate bond strength. Several studies have demonstrated long-term bond strength retention [29,30]. Research also shows that incorporating CHX into the etchant results in a smaller reduction in microtensile bond strength (μTBS) compared to the control group. Loguercio et al. [29] observed, using Raman spectroscopy, that CHX molecules remained within the hybrid layer even after five years.

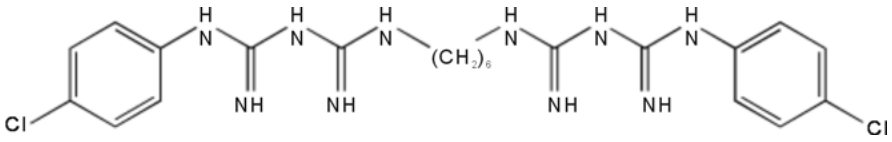

Figure 3: Molecular formula of CHX

VI. BENZALKONIUM CHLORIDE (BAC) AS MMP INHIBITOR:

Benzalkonium chloride (BAC) is a quaternary ammonium compound with a cationic (positively charged) nature, which gives it a strong attraction to the negatively charged carboxylic groups in collagen [20]. Sabatini et al. observed that the experimental researches consulted with BAC exhibited higher microtensile bond strength (μTBS) than the control group, both at 24 hours and after 6 months. Benzalkonium chloride (BAC) has been

investigated as a matrix metalloproteinase (MMP) inhibitor in dentistry [22]. MMPs are enzymes that can degrade extracellular matrix components, including collagen in dentin, which can compromise the durability of dental adhesives. Studies have shown that BAC can effectively deactivate MMPs in demineralized dentin, leading to a reduction in their enzymatic activity in a dose-dependent manner. By applying BAC, researchers have observed significant reductions in total MMP activity, which helps to preserve the structural integrity of dentin and improve the longevity of adhesive bonds. In addition to its immediate effects, BAC-containing adhesives can provide sustained reduction of MMP activity over time. However, some studies have also noted that under certain conditions, BAC may lead to an increase in gelatinolytic activity and a decrease in bond strength, suggesting that careful optimization of concentration and application is crucial for achieving the desired benefits without adverse effects. Overall, BAC shows promise as an MMP inhibitor in dental applications, potentially enhancing the effectiveness of dental adhesives.

VII. PROANTHOCYANIDINS AS MMP INHIBITOR:

Proanthocyanidins are plant-derived polyphenols known for their antioxidant properties and ability to interact with various biological molecules. Proanthocyanidins can inhibit MMP activity, thereby preventing collagen breakdown and contributing to the stability of the dentin structure. Utilizing proanthocyanidins in dental treatments may improve the longevity of restorations and the natural resilience of dentin, making it a promising area for future research and clinical application. Proanthocyanidin (PA), a flavonoid in the polyphenolic compound category, offers significant health benefits for humans. Typically sourced from grape seeds and blueberries, PA is often extracted for its uses [23]. It is recognized for its ability to reduce oxidative stress [24] and has been extensively studied for its antimicrobial properties [25,26]. These antimicrobial and anti-inflammatory characteristics have garnered interest within the dental community. Dias et al. investigated the microtensile bond strength (μTBS) of a bonding with varying concentrations of PA—0%, 1%, 2%, 4.5%, and 6%—both immediately and after 12 months of storage [27,28,29]. They found that incorporating 2%, 4.5%, and 6% PA preserved the μTBS of dentin even after one year, without negatively influences the solubility, sorption, and degree of conversion of the adhesives [27]. Moreover, treating demineralized dentin with nanohydroxyapatite (PA) may offer a promising approach to enhance its strength by stabilizing the collagen and providing additional reinforcement.

VIII. EPIGALLOCATECHIN-3-GALLATE (EGCG):

Epigallocatechin gallate (EGCG) is a polyphenol found in high concentrations in some of the tea leaves and it is considered as the main green tea catechin [31]. Previous studies have demonstrated that the green tea can inhibit MMP activity and the activation of proMMP-2[32]. According to Gerhardt et al., applying EGCG at a 2% concentration applied to dentin improved the adhesive bond strength of a self-etching adhesive to traditional dentin. Multiple researches have indicated that incorporating EGCG into adhesive systems leads to consistent and stable bond strength over time. However, Amaral FL et al. observed a decline in adhesion strength values after the following six months, regardless of the type of dentin treatment used**.** The compound EGCG has been found to modulate numerous disease-related molecular targets. However, many of these targets are influenced only by EGCG concentrations that exceed what can be obtained through regular green tea consumption or moderate doses of green tea extract supplements.

IX. CONCLUSION:

Matrix metalloproteinases (MMPs) and their inhibitors play a multifaceted role, dual-edged function in restorative dentistry. While MMPs contribute to the degradation of dental tissues and adhesive interfaces, leading to material failure and compromised longevity of restorations, they also have potential therapeutic applications in enhancing tissue healing and regeneration. Using MMP inhibitors offers a promising approach to prevent the enzymatic breakdown of dentin-resin bonds, thereby enhancing the longevity of adhesive restorations. However, the clinical implementation of MMP inhibitors must be carefully balanced, as over-inhibition could interfere with normal tissue remodeling and wound healing processes. Future research should focus on developing more targeted and controlled methods of MMP inhibition, optimizing their clinical use in restorative procedures. Clinicians must also stay informed about the evolving understanding of MMP dynamics in dental tissues to make evidence-based decisions on when and how to incorporate MMP inhibitors into treatment protocols. Overall, the nuanced role of MMPs and their inhibitors in restorative dentistry highlights the importance of a personalized, case-specific approach to ensure both the short- and long-term success of dental restorations.

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