MMP inhibitors –A review

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Introduction :

Matrix Metallo Proteinases (MMPs) are a cell-derived proteolytic enzyme family with 26 identified members [1]. Specific enzymes of this family can function beneficially during tissue remodeling and during formation of the extra cellular matrix or the mineralization of dentin [2]. However, MMPs can act during inflammation to increase the adverse effects of cardiovascular disease [3], cancer metastasis [4], periodontal disease and the carious process by destruction of the collagen and other proteins of the extra cellular matrix. Normally, the protein cleavage activity of MMPs is balanced in time and spatially by cell secreted inhibitors called Tissue Inhibitors of Metalloproteinases (TIMPs). If the balance is disturbed inflammation, arthritis, cancer and heart problems become manifest [5]

Structure of MMP :

MMPs are a large family of calcium‐dependent zinc‐containing endopeptidases, which are responsible for the tissue remodeling and degradation of the ECM, including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan. MMPs are usually minimally expressed in normal physiological conditions, and thus homeostasis is maintained. However, MMPs are regulated by hormones, growth factors, and cytokines, and are involved in ovarian function [6].Endogenous MMP inhibitors (MMPIs) and tissue inhibitors of MMPs (TIMPs) strictly control these enzymes. Overexpression of MMPs results in an imbalance between the activity of MMPs and TIMPs that can lead to a variety of pathological disorders [7]. The earliest descriptions of MMPs were in 1949 as depolymerizing enzymes which, it was proposed, could facilitate tumor growth by making connective tissue stroma, including that of small blood vessels, more fluid. [8] About after 13 years, the first vertebrate MMP, collagenase, was isolated and characterized as the enzyme responsible for the resorption by tadpole tail. During the next 20 years, several mammalian enzymes were partially purified, but it was not until 1985 that the field really developed when structural homologies became apparent, allowing many new members to be identified through the techniques of molecular biology.[9-11]

Classification of MMP's:

Metal‐binding proteinases represent a relatively large and evergrowing group of enzymes.Researchers have proposed dividing this class of MMPs into clans (based on similarity of protein fold) and families (based on evolutionary relationships).Currently, the MMP class comprises eight clans and some 40 families [12]. The MMP family is a continually growing group, now comprising more than 20 enzymes.There are two classification systems of the MMPs: The availability of the complete human genome sequence has allowed defining the complete set of MMPs produced by human cells. Thus, recent genomic studies have revealed that there are 24 distinct genes encoding members of

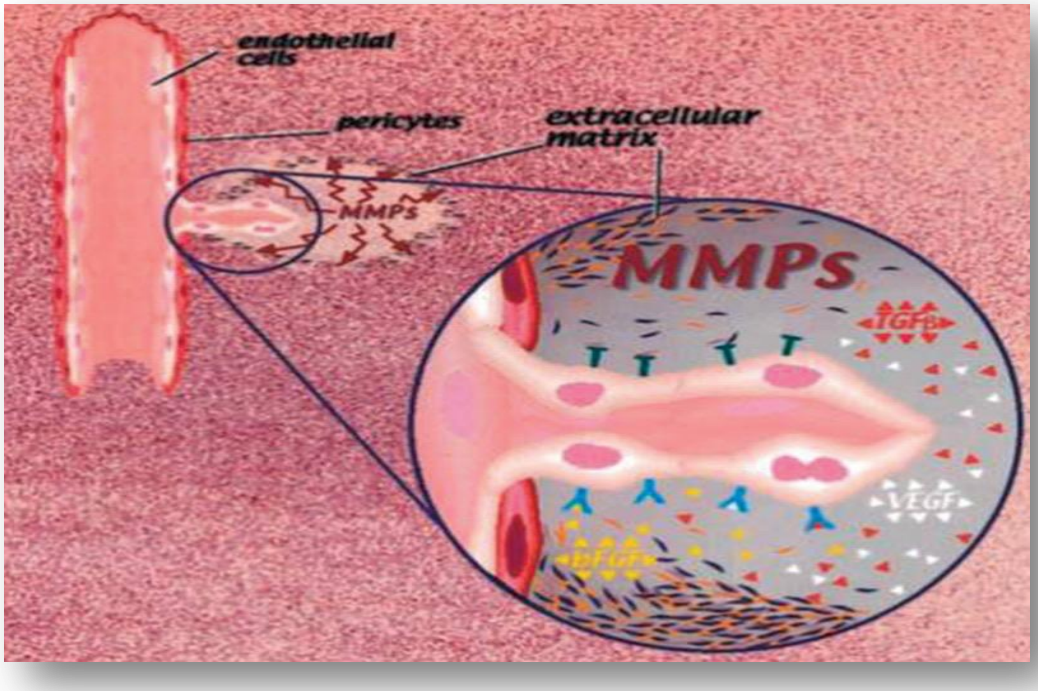
the MMP family[13].Analysis of the structural design of these enzymes has led to a new classification system based on MMP structures rather than on their substrate specificities

Table 1 - List of known MMPs and their substrates (from Lynch and Matrisian, 2002).

MMP	Alternative name	ECM substrate	Non-matrix substrates
MMP-1	Collagenase-1	Collagen I/II/III/VII/X/XI, gelatin, entactin, aggrecan, fibronectin, laminin, tenascin, vitronectin	Perlecan, IGFBP-2/3, ProTNF-α, α1-AC, α2-MG, α1-PI
MMP-2	Gelatinase A	Collagen I/III/IV/V/VII/X/XI, tenascin decorin, gelatin, elastin, fibronectin, laminin, aggrecan, vitronectin	TGF-β, TGF-β2, IL-1β, MCP-3, SDF-1, IGFBP-3/5, TNF-α, FGF-R1, α1-AC, α1-PI
MMP-3	Stromelysin-1	Collagen III/IV/V/VII/IX/X/XI, elastin, laminin, fibronectin, gelatin, aggrecan entactin, decorin, tenascin, vitronectin	Perlecan, HB-EGF, IL-1β, plasminogen, E-cadherin, IGFBP-3, TNF-α, α1-AC, α2-MG, α1-PI
MMP-7	Matrilysin	Collagen I/IV, aggrecan, laminin, fibronectin, gelatin, entactin, decorin, elastin, tenascin, vitronectin	FASL, β4 integrin, E-cadherin, HB-EGF, plasminogen, TNF-α, α1-PI
MMP-8	Collagenase-2	Collagen I/II/III, aggrecan	α2-MG, α1-PI
MMP-9	Gelatinase B	Collagen IV/V/XI/XIV, decorin, gelatin, elastin, laminin, aggrecan, vitronectin	TGF-β2, IL-1β, TNF-α, IL-2Ra, plasminogen, α1-AC, α2-MG, α1-PI
MMP-10	Stromelysin-2	Collagen III/IV/V, aggrecan, elastin, laminin, fibronectin, gelatin	ND
MMP-11	Stromelysin-3	ND	IGFBP-1, α2-MG, α1-PI
MMP-12	Metalloelastase	Collagen I/IV, aggrecan, decorin, gelatin, elastin, fibronectin, laminin, vitronectin, entactin	Plasminogen, α2-MG, α1-PI
MMP-13	Collagenase-3	Collagen I/II/III/VI/IX/X/XIV, gelatin, fibronectin, aggrecan	α2-MG
MMP-14	MT1-MMP	Collagen I/II/III, gelatin, fibronectin, laminin, entactin, vitronectin, aggrecan	CD44, transglutaminase, α2-MG, α1-PI
MMP-15	MT2-MMP	Aggrecan, entactin, fibronectin, laminin, tenascin	Transglutaminase
MMP-16	MT3-MMP	Collagen III, fibronectin, gelatin	Transglutaminase
MMP-17	MT4-MMP	Gelatin	α2-MG, TNF-α
MMP-18	Collagenase-4 (Xenopus)	Collagen I	ND
MMP-19	RASI	Collagen I/IV, fibronectin, gelatin, tenascin, laminin, aggrecan, entactin, COMP	ND
MMP-20	Enamelysin	Collagen X VIII, aggrecan, amelogenin, COMP	ND
MMP-21	XMMP (Xenopus)	No known substrates	ND
MMP-22	CMMP (chicken)	Gelatin	ND
MMP-23	CA-MMP (cysteine array MMP)	ND	ND
MMP-24	MT5-MMP	Collagen I, gelatin, fibronectin, laminin	ND
MMP-25	MT6-MMP	Collagen IV, gelatin, fibronectin	ND
MMP-26	Matrilysin-2	Collagen IV, fibronectin, gelatin	α1-PI
MMP-27	Endometase	ND	ND
MMP-28	Epilysin	ND	ND

MMP and Cancer:

The expression and activity of MMPs are increased in almost every type of human cancer; and this correlates with advanced tumor stage, increased invasion and metastasis, and shortened survival. Early expression of MMPs, either by the tumor cells themselves or by surrounding stromal cells, helps to remodel the ECM and release ECM and/or membrane-bound growth factors, which provides a favorable microenvironment for the establishment of the primary tumor [Figure 1]. Also there are increasing evidence suggesting that MMPs regulate tumor growth by favoring the release of cell proliferating factors such as insulin-like growth factor (IGF) which binds to specific-binding protein. MMPs activities have also been traditionally associated with variety of escaping mechanism that cancer cell develop to avoid host immune response[14].MMPs degrade components of ECM, facilitating angiogenesis, tumor cell invasion, and metastasis. MMPs modulate the interactions between tumor cells by cleaving E-cadherin, and between tumor cells and ECM by processing integrins, which also enhances the invasiveness of tumor cells [15]. MMPs also process and activate signaling molecules, including growth factors and cytokines, making these factors more accessible to target cells by either liberating them from the ECM (e. g., VEGF and bFGF) and inhibitory complexes (e. g. TGF), or by



shedding them from cell surface (e. g., heparin-binding epidermal growth factor)

Given the important roles that MMPs play in tumor growth, metastasis, and the dysregulated angiogenesis that drives them; there has been significant attention paid to the development of clinically useful antagonists of this enzyme family. There are a number of MMPIs that are currently being tested against a variety of human.[16]

The promise of this therapeutic approach has yet to be realized and the academic, pharmaceutical, and biotechnology arenas continue to debate the potential issues underlying the lack of therapeutic success in cancer treatment. Although certainly not in the majority, there have been some promising results from some clinical trials.

MMPs in oral mucosal lesions :

The role of MMPs has been investigated in a number of skin conditions that can also involve the mucosal surfaces like: Lichen planus (LP), discoid lupus erythematosus (DLE),

Table 4: Role of MMPs in mucocutaneous lesions

Skin disorders	MMPs expressed
Lichen planus and discoid lupus erythematosus	MMP-1, 2, 3* MMP-9**
Systemic lupus erythematosus, DLE, subacute cutaneous LE	MMP-3,10,19, 26**, TIMP-1*, TIMP-3** (imbalance between MMPs and their inhibitor lead to degradation of epidermis)
Autoimmune dermal conditions (pemphigus vulgaris, bullous pemphigoid, and pemphigus foliaceus)	MMP-2, 3, 9** (overexpression in dermis and under expression in epidermis)
Stevens-Johnson syndrome and toxic epidermal necrolysis are two forms of hypersensitivity condition that leads to mucosal damage and blistering	MMP-2, 9**
Dermatitis herpetiformis	MMP-12**
Recurrent apthous ulceration	MMP-1, 2, 39, 12

*Low expression, **high expression. MMP=Matrix metalloproteinase, DLE=Discoid lupus erythematosus, TIMP=Tissue inhibitors of MMP

psoriasis, pemphigus, and pemphigoid. Various studies [17] have shown that MMPs mediate the inflammatory response and induce dermal destruction .

Dental Caries and Role of MMPs in Caries Progression :

Dental caries is an irreversible disease of calcified tissue of teeth, characterized by demineralization and subsequent destruction of the organic substance of the tooth, finally leading to cavitation. The progression of caries into dentin requires bacterial invasion along the dentinoenamel junction [18].The lengthening of the initial lesion with the destruction of the mantle dentin has also been described.During the demineralization phase of dental caries, hydroxyapatite is solubilized by organic acids produced by oral bacteria[19-21]. Bacterial organic acids can diffuse into calcified dental tissues when the local pH falls to below 5.5, leading to dissolution of the mineral crystals .The dynamic process of demineralization that occurs numerous times daily is usually balanced by the buffering potential of the saliva that allows remineralization to occur. However, if this balance is lost, pathological factors predominate, and caries progression takes place. Caries progression induces several modifications to dentin (reduction of mineral content, increase in micro- and nano-porosities due to changes in dentin collagen structure and distribution and noncollagenous protein), synergistically contributing to reductions in physical and

mechanical dentin properties .In dentin, demineralization is followed by destruction of the collagenous organic matrix of dentin, long thought to be caused by bacterial proteases. However, cariogenic bacteria do not degrade dentin matrix after they have demineralized it [22].Furthermore, the bacteria collected from dentinal lesions created in situ are not capable of degrading collagen in vitro, and even purified bacterial collagenases have low activity in acidic environments.Since the evidence of bacterial input to the degradation of the organic matrix of carious dentin is lacking, it has more recently been thought to be mediated mainly by host-derived MMPs .The increase of MMPs (and possibly cysteine cathepsins) in dentinal fluid under caries lesions and MMPs [23] originating from saliva may be behind the markedly higher enzyme activity levels in carious than in normal dentin.

MMP inhibitors :

Therapeutic MMP Inhibitors in Caries Progression and Bond Stability Lately, a growing interest in dental research has been focused on screening MMP inhibitors from different sources and how they might promote dental caries prevention and remineralization . In addition, several strategies to retain the integrity of the HL and improve the long-term dentin bond strength have been proposed [24].MMP activity in dentin matrices can be reduced by endogenous and exogenous inhibitors. Endogenous inhibitors originate from different human cells, while exogenous inhibitors are synthesized as therapeutic agents. Most of these inhibitors chelate calcium or replace the zinc ions at the active site and/or interact with the MMP propeptide fragment, while others may prevent MMP access and inhibit activity by coating the substrate. It has been previously shown in animal experiments that MMP inhibition can reduce dentinal caries progression.Chemically modified tetracycline-3 (CMT-3) and zoledronate (a bisphosphonate with MMP-inhibiting activity) reduced rat molar dentinal caries by 60% to 87% .CMT-5, a tetracycline analogue with a very low MMP-inhibitory effect compared with CMT-3, had practically no effect of rat molar caries.CMT-3 also eliminates the human salivary gelatinase activity,and systemic doxycycline medication has a similar effect on salivary collagenase activity [25,26].These data further support the importance of MMPs in the development and progression of dentin caries. Similarly, indirect proof of the role of MMPs in the stability of the HL over time has been reported by several studies, showing increased bond strength and reduced interfacial degradation over time if MP inhibitors were used during the bonding procedure [27] .Chlorhexidine, tetracycline, galardin ,benzalkonium chloride and quaternary ammonium methacrylates are just some of the tested MMP inhibitors showing positive effects on bond strength stability. Indeed, the most tested inhibitor is CHX, which effectively reduces the activity of MMP-2,9, and 8 cysteine cathepsins . Even at concentrations as low as 0.2%, CHX showed bond strength preservation and reduced interfacial degradation (i.e., reduced nanoleakage expression). CHX inhibition of proteases may be related to its cation chelating property, and calcium ions released by adhesive primers may be responsible for the loss of inhibition by CHX over time. Because of this limitation (leaching and recharge of ions), collagen cross-linker agents have recently been proposed as a more permanent way of inactivating protease enzymes [28].

Role of MMP inhibitors in dentin :

Major concerns have been expressed recently regarding the long-term dentin bonding of resin adhesives. Long-term bonding is threatened by disaggregation of the hybrid layer owing mainly to the activation of dentin MMPs. Several methods have been suggested to achieve superior infiltration of monomers, to inhibit the breakdown of collagen fibrils, and to reduce aging water sorption, for example: using hydrophobic adhesives following the use of all-in-one adhesive primers, which have a low level of water sorption and

solubility application of multiple layers , lengthening the curing time , increasing solvent evaporation and using electric current [29]. Alternatively, it would be advantageous from a clinical perspective to be able to inhibit the break- down of deficient resin-impregnation collagen fibrils by host-derived MMPs in the dentinal hybrid layer. Tissue inhibitors of metalloproteinases (TIMPs) are the major endogenous inhibitors of MMPs. The balance between MMPs and TIMPs, which is important for tissue ECM remodelling, is destroyed in many diseases [30].Both increasing the local concentration of TIMPs and application of extrinsic MMPs inhibitors can be used to recover the MMP-TIMP balance and thereby block disease progression. Protease inhibitors as additional primers might be recommended to inhibit the intrinsic collagenolytic activity of human dentin, to reduce the aging of bonding interfaces and to increase the stability of the dentinal collagen fibrils within the hybrid layer [31].This is essential in dentin bonding and may be achieved by inhibiting activated host-derived dentin enzymes which are liable for the breakage of dentin collagen fibrils without bacteria. The activities of endogenous collagenase and gelatinase derived from demineralized dentin are thought to induce the degradation of bonded dentin matrix in the hybrid layer. Therefore, the application of some specific MMP inhibitors which can suppress dentin collagenolytic and gelatinolytic activities ,such as EDTA and chlorhexidine were recommended to restrict the deterio- ration of hybrid layers. Even very low chlorhexidine concentrations showed complete MMP inhibition.[32]

The MMPs are a class of zinc and calcium de- pendent endopeptidases, which are trapped within the mineralized dentin matrix during tooth development . The release and subsequent activation of these endogenous enzymes during dental restorative procedures are believed to be responsible of the dentin adhesive bonding failure.[33]In fact it was observed in an in vitro study the thinning and the disappearance of collagen fibrils from not fully infiltrated hybrid layers after dentin treatment with adhesive.Despite the different adhesive procedures, the result is often an incomplete hybridization of the dentin surface, so the collagen fibrils remain unprotected from factors promoting hydrolytic degradation, as the residual solvent of the adhesive or the water not removed from the dentin surface.[34]Recent studies have revealed the contribution of host protease in the degradation of matrix collagen in the pathogenesis of dentin caries and periodontal disease, with potential implications in dentine bond interface.[35]The nanoleakage may also occur in the absence of gaps along the adhesive dentin in- terface, this suggests that the degradation of not fully infiltrated dentin by host proteinases may proceed in absence of bacterial enzymes. The matrix of etched dentin may be slowly degraded over time by proteolytic enzymes derived from dentine itself, in the absence of bacteria Intrinsic collagenolytic activity in human mineralized dentin can be inhibited by spe- cific inhibitors of protease. The presence of collagenolytic and gelatinolytic activity in partially demineralized dentin is an in- direct evidence of the existence of matrix metal- loproteinases (MMP) in human dentin ,in fact, the presence of gelatinases (MMP-2).
and MMP-9), collagenase (MMP-8) and enamelysine (MMP-20) and in demineralized dentin has been demonstrated through zymography and Western blotting techniques.[36]
Recently has been discovery cysteine cathepsins in normal and carious dentin .Cysteine cathepsins are papain-like endopeptidases that participate in intracellular proteolysis within the lysosomal compartments of living cells . These endogenous enzymes are latent forms of MMPs (pro-MMPs) via the cysteine-switch mechanism that exposes the catalytic domain of these enzymes that were blocked by propeptides . Cathepsins are responsible for the digestion of collagen fibrils exposed at the adhesive interface.The collagen degradation occurs at the bottom of hybrid layer and was also observed in vivo studies. Unfortunately, it was not yet es- tablished a relationship between the different etch&rinse techniques and the degradation of dentin hybrid layers. [37].Presumably, the dentin conditioning with phosphoric acid could

inhibit the MMPs that are entrapped in the mineralized dentin. The potential role of dentin adhesives in proteolysis activation using a modelling approach in which the relative dentin proteolytic activities were quantified before and after the sequential application of orthophosphoric acid and total etch adhesive. The total-etch adhesives can activate dentin MMPs that have been previously neutralized by orthophosphoric acid etchant.[38]. The gelatinolytic and collagenolytic activity of dentin can be neutralized from MMPs inhibitors, in fact to reduce the aging of bonding interfaces and to increase the stability of the hybrid layer, the protease inhibitors as additional primers might be recommended.[39]

Chlorhexidine

Chlorhexidine is now used in adhesive dentistry as an inhibitor of MMPs this chemoterapeutic agent is commonly used in Periodontology as antiseptic agent in mouthrinse. CHX is the first candidate to be test- ed in attempts to inhibit collagenolytic enzymes in dentin .CHX had been demonstrated to effectively inhibit MMP-2, -9 and -8 . CHX, applied on etched human dentin, has MMPs inhibitory properties: its capacity leads to the protection of the integrity of the hybrid layer collagen after application of the etch & rinse adhesive, confirming the indirect involvement of MMPs in the degradation of collagen.The effective concentrations have varied between 0.002% and 4%, 0.2% and 2%. The best concentration common used is the 2%.The application of chlorhexidine improves the integrity of the hybrid layer achieving the com- plete inhibition of the proteolytic enzymes . In fact, when phosphoric acid is applied without the subsequent application of chlorhexidine, the collagenolytic activity of mineralized dentin is not inhibited, while the use of CHX after dentin etching strongly inhibited this activity. This is asserted in study in which are compared the effect of the application of a total- etch adhesive, the Adper Scotchbond 1XT (SB1XT), with and without 0,2-2% CHX pre- treatment for 30s on the etched surface Zymograms showed that application of SB1XT to human dentin powder increases MMP-2 activity, while CHX pre-treatment inhibited all dentin gelatinolytic activity, irrespective from the test- ed concentration. CHX significantly lowered the loss of bond strength and nanoleakage seen. in acid-etched resin-bonded dentin artificially aged for 2 years . For etch-and-rinse adhesives, CHX may be applied to the demineralized dentin directly or in- corporated into an acid conditioner prior to the application of adhesives, which has been shown to be effective for reducing degradation of resin-dentin bonds after in vivo aging. Recently, A study suggests the power of chlorhexidine to inhibit cysteine cathepsins which may also contribute to its effect on preserving hybrid layer collagen.[35,40-42]

EDTA:

EDTA (ethylenediaminetetraacetic acid) is an endodontic chelant with the capacity to in- activate endogenous MMP activity in human dentin.In fact MMPs activity of dentin demineralized beams with phosphoric acid, which also activat- ed endogenous MMPs, and divided into 4 experimental groups on the basis of exposure time to 17% EDTA (0, 1, 2, or 5 minutes).[43]. The study asserted that 17% EDTA significantly inhibits endogenous MMP activity of human dentin within 1-2 minutes.[44]This might minimize hybrid layer degradation after resin bonding procedure

Carbodimide:

Carbodiimide (1-Ethyl-3-[3-dimethylamino propyl] carbodiimide Hydrochloride, or EDC) is a stable cyanamide isomer.[45] The EDC is able to improve the stability of the dentine bondin thanks to its cross-linking capacity. Its mechanism of collagen cross-linking involves

the activation of the carboxylic acid groups of glutamic and aspartic acid residues .The EDC has great potential to enhance the stability of the interface, most likely due to increased mechanical properties of the dentin matrix and slower degradation rates of collagen .So it is possible to assert that EDC can produce long-term inactivation of MMPs in acid-etched dentin matrices contributing to bond strength preservation over time.[46] As assayed with the zymography the EDC pretreatment inhibited dentin endogenous MMPs.

Chitosan:

Chitosan is a natural polysaccharide biopolymer composed by β-(1-4)-linked D-glu- cosamine (deacetylated unit) and N-acetyl-D-glu- cosamine (acetylated unit). Chitosan owns anti- bacterial property related partly to the interaction between positively charged chitosan and negatively charged bacterial cell surface that would de- crease bacterial cell permeability, resulting in cell death. [47]The modification of the bonding substrate with chitosan and riboflavin increases the mechanical properties, enhanced the mechanical stability of demineralized dentin substrates against hydrolytic and collagenolytic degradation of the MMPs. The gradual increase in chitosan contents permits a major obliteration of interfibrillar-spaces that might adversely affect bonding to dentin [48,49].

ZnO:

Synthetic peptidomimetic inhibitors with zinc chelator properties can be used to inhibit the active site of the catalytic domain, thus inhibiting the activity of MMPs .Addition of ZnO particles to dental adhesives produced a minor dentine collagen degradation and an increasing of resin-dentine bonds durability: so it is possible to preserve the adhesives bonding efficacy overtime.[50]

Tetracycline:

Tetracyclines are antibiotics commonly used in the treatment of periodontitis. Tetracyclines and their semisynthetic forms, doxicycline (DO) have the ability to inhibit MMPs collagen degradation activity.[51] The dentin surface pre-treatment, after the etching procedures, with an aqueous solutions of 2% doxycycline can inhibit collagenases and gelatinases, determining an improvement of dental bonding. DO cannot be used with acetone based adhesive systems, because lower bond strength values as well as higher silver nitrate penetration were observed within the hybrid layer. Also the deriva tives and chemically modified analogs (chemically modified tetracyclines, CMTs) showed the potential to inhibit the collagenolytic degrada- tion of the MMPs.The most potent CMTs against collagenases is CMT-3 (aka Metastat, COL-3) but it is also effective against gelatinases, and is particularly effective in inhibiting MMPs in dentinal caries lesions .[52]

Galardin:

Galardin is a synthetic MMPs inhibitor . Galardin has a collagen-like backbone and a hydroxamate structure (R-CO-NH-OH) which chelates the zinc-ion located in the catalytic domain MMPs. The bonding surface treated with 0.2 mM galardin water solution showed a slowed decline of bond strength and reduced the amount of nanoleakage, but it did not completely block these phenomena.[53]

Other MMP inhibitors :

It has also been discovered that proanthocyanidins a grape seed extract, has the a promising approach to improving the durability of current dentin bonding systems[54].

Conclusion:

The dentin adhesive procedures have undergone revolutionary changes in recent decades. Despite the countless studies and the discovery of new more versatile materials, even today, the adhesive interface remains the weak point of the adhesive tooth-restoration complex. Unfortunately, it is also the most vulnerable part of the restoration, because it is influenced by nanolekeage, micropermeability and by the degradation of metalloproteases.[55] The gelatinolytic and collagenolytic activity of dentin can be neutralized from protease inhibitors, which means that inhibition of MMPs could preserve the integrity of the hybrid layer. A partial solution to the problem of hybrid layer deterioration may be the incorporation of appropriate MMPs inhibitors into adhesive bonding systems. Water sorption of adhesive interfaces most likely remains the principal mechanism of bond degradation, while endogenous enzymes appear to contribute to bond degradation of only total etch adhesives. The degradation of collagen fibrils in situ within an incompletely infiltrated hybrid layer has been shown to have an adverse effect on the remineralization of unprotected dentin collagen in vivo [56] .MMP inhibitors, which prevent collagen degradation during dentinal caries, should be recommended for use in the natural healing of carious dentin matrix through further remineralization. During the dentin bonding process, it would be advantageous to apply MMP inhibitors that have the ability not only to inhibit the breakdown of dentin collagen within the hybrid layers, thereby improving the durability of dentin bonding, but also to prevent the occurrence of secondary caries around restorations [57].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.Thus this review has highlighted on the various MMP inhibitors and its action .

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