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FIFTH STAGE

The role of matrix metaloprotienases (mmps) in humen dental caris and peri apical inflamation

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Dedication

To my family, the reason of what I become today Thanks for your great support and continues care.

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ACKNOWLEDGEMENTS

First of all, Praise be to God for what He has bestowed upon Him, and to Him is gratitude for what He has inspired.
After that, we would like to extend our sincere thanks to the Deanship of the Faculty of Dentistry, Maysan University, represented by the Dean, the heads of departments and the teaching staff for the dedication that was offered to get us to this stage. We would also like to extend our sincere thanks to our honourable professor, Dr. Khaled Jabbar, for his effective role and his constant perseverance in providing us with all the useful and valuable information throughout this journey.
Last but not least, we extend our heartfelt thanks and gratitude to everyone who contributed to the realization and completion of this project.

Introduction:

One of the most common oral diseases is dental caries. Oral health has remained as an integral part of an individual's general health and over all wellbeing. Good oral health practices are necessary from a young age to ensure positive long term dental health and hygiene.

Dental caries remains a major oral health disease-affecting children worldwide. About 90% of school children worldwide and most adults have experienced caries, with the disease being most prevalent in Asian and Latin American countries. The rate of caries prevalence is 76.3% and the incidence of dental caries was found to be highest in the age group of 16 years.

Caries can occur throughout life, both in primary and permanent dentitions, and can damage the tooth crown and, in later life, also exposed root surfaces. The balance between pathological and protective factors influences the initiation and progression of caries. Pitts, N. B.2017.

Dental caries is known as a multi factorial disease.
The factors can be divided into 3 types which are personal factors, oral environmental factors and also factors that directly contribute to caries development. Many researchers

The aim of study:

To find out the role of matrix metaloprotienases (mmps) in humen dental caries and peri apical inflamation

Review:

Normal Tooth Anatomy

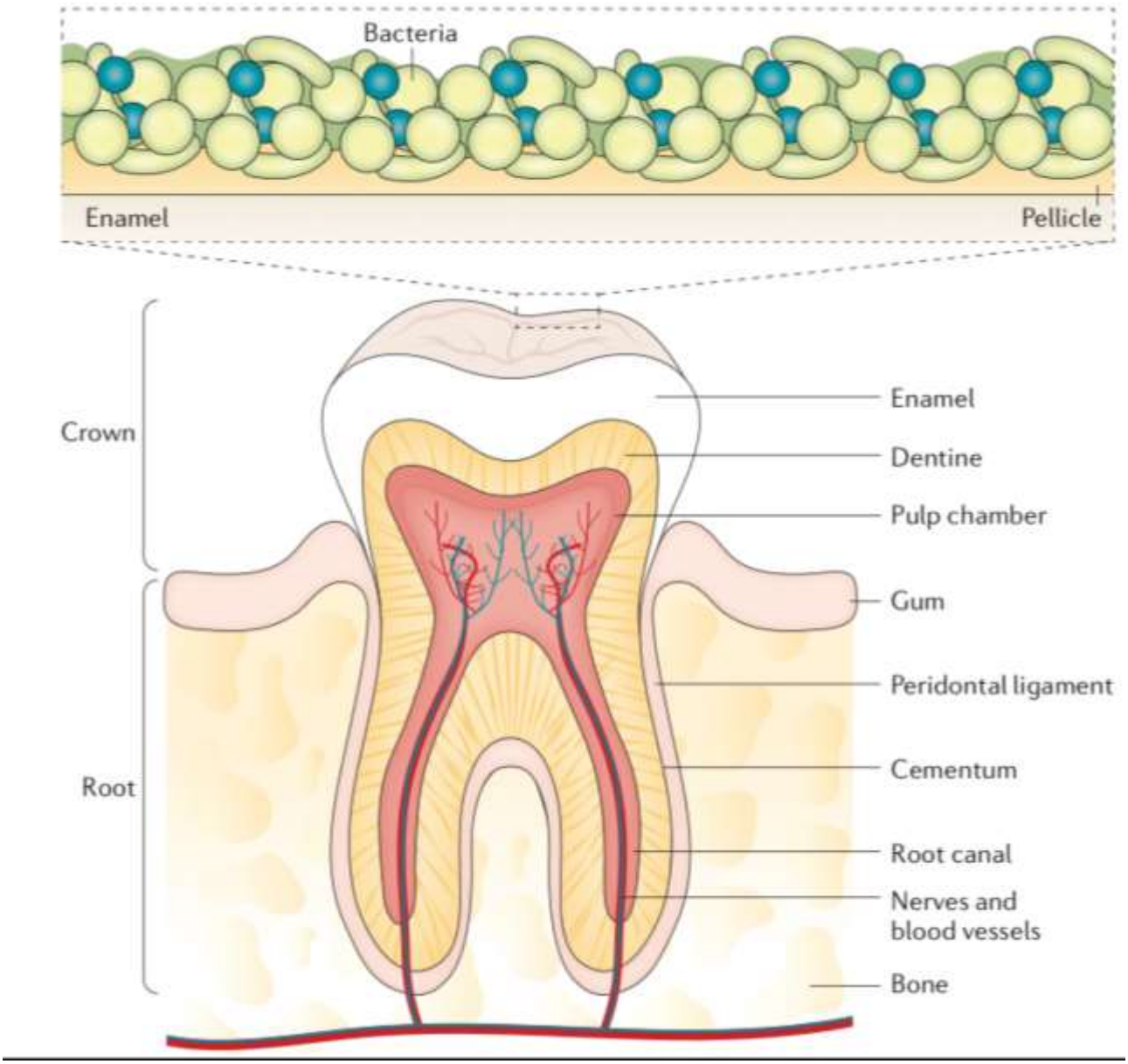

Figure 1

In figure (1), normal tooth anatomy and developing dental biofilm. The hard tissue of the tooth consists of enamel, dentine and cementum. Enamel is a hard material composed almost exclusively of mineral — which is mainly composed of hydroxyapatite (Ca10 Nature Reviews | Disease Primers (PO4)6(OH)2) — and covers the dentine on the crown of the tooth. Cementum is a bone-matrix-like substance, composed of mineral and collagen; it covers the root of the tooth. The dental pulp forms the central part and contains connective tissue, blood vessels and nerves. Teeth are covered by a salivary pellicle layer, consisting of proteins and glycoproteins, which facilitates binding of the oral microbiota to the teeth; this structure is called the dental biofilm (also known as dental plaque). The biofilm shuts off the surface enamel from the saliva and oral cavity and produces a protected microenvironment at the tooth surface.

Dental caries:

Dental caries is the most prevalent chronic disease worldwide. It's an infectious disease characterized by a multifactorial etiology and slow evolution that leads to the destruction of dental hard tissues.

It's involves intervactions between the tooth structure, the microbial biofilm formed on the tooth surface) an imbalance of oral microflora—normally more than 700 different species—leads to an increase in the cariogenic bacteria mainly Streptococcus mutans and Lactobacillus types) and sugars, as well as salivary and genetic influences. The dynamic caries process consists of rapidly alternating periods of tooth demineralization and remin-eralization, which, if net demineralization occurs over sufficient time, results in the initiation of specific caries lesions at certain anatomical predilection sites on the teeth. It is important to balance the pathological and protective factors that influence the initiation and progression of dental caries. Protective factors promote remineraliza-tion and lesion arrest, whereas pathological factors shift the balance in the direction of dental caries and disease progression (Pitts, N.B. & Zero, D.T (2016).

the oral microbiome influences the formation of dental caries, many host factors including teeth and saliva also affect caries development, leading to a disease that tends to be chronic and slowly progressive. The dental biofilm is an important component in the etiology of dental caries. Numerous studies have reported that controlling the dental biofilm is the key to preventing tooth decay (Bioact. Mater. 2019).

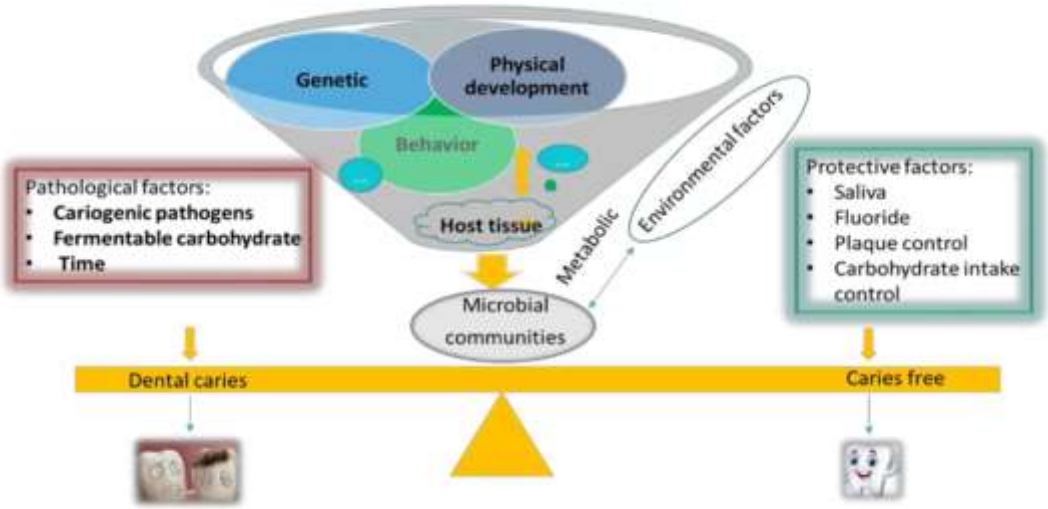

Figure 2

Etiology of dental caries:

1-Tooth (morphology, site, composition)
2- Substrate (Enviromental factors): -
i- saliva. Include: -
a- Composition.
b- Quantity.
c- pH.
d- Viscosity.
e- Antibacterial factors.
Ii-Diet include: - Carbohydrate,
Vitamin content, Fluoride content and
Fat content.
3-Microorganisms.
4- Time period.

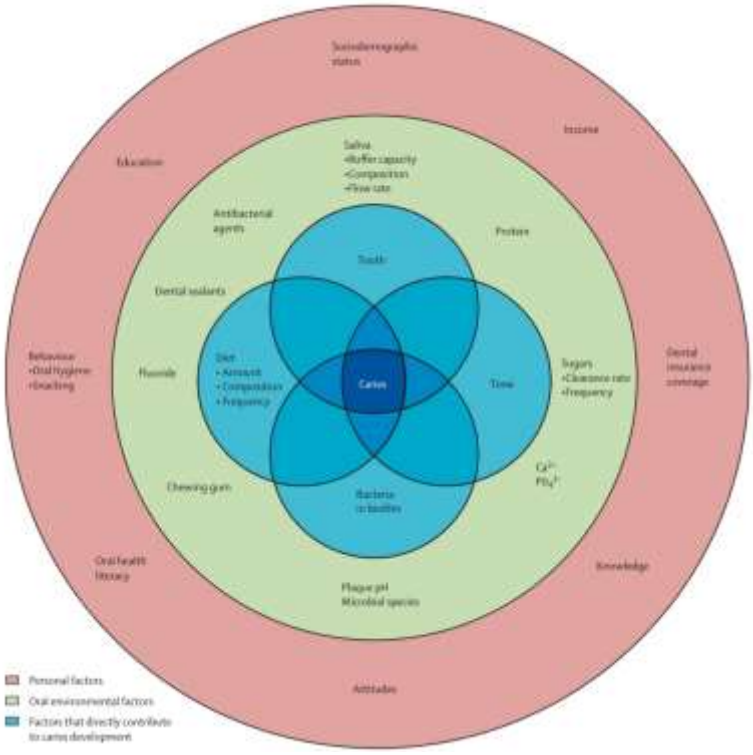

Figure 3

Stages of dental caries:

Stage 1: Initial demineralization

The outer layer of your teeth is composed of a type of tissue called enamel. Enamel is the hardest tissue in your body and is mostly made up of minerals.
However, as a tooth is exposed to acids produced by plaque bacteria, the enamel begins to lose these minerals.
When this occurs, you may see a white spot appear on one of your teeth. This area of mineral loss is an initial sign of tooth decay.

Stage 2: Enamel decay

If the process of tooth decay is allowed to continue, enamel will break down further. You may notice that a white spot on a tooth darkens to a brownish colour. As enamel is weakened, small holes in your teeth called cavities, or dental caries, can form. Cavities will need to be filled by your dentist.

Stage 3: Dentin decay

Dentin is the tissue that lies under the enamel. It's softer than enamel, which makes it more sensitive to damage from acid. Because of this, tooth decay proceeds at a faster rate when it reaches the dentin. Dentin also contains tubes that lead to the nerves of the tooth. Because of this, when dentin is affected by tooth decay, you may begin experiencing sensitivity. You may notice this particularly when having hot or cold foods or drinks.

Stage 4: Pulp damage

The pulp is the innermost layer of your tooth. It contains the nerves and blood vessels that help to keep the tooth healthy. The nerves present in the pulp also provide sensation to the tooth.
When damage to the pulp happens, it may become irritated and start to swell. Because the surrounding tissues in the tooth can't expand to accommodate this swelling, pressure may be placed on the nerves. This can lead to pain.
A tooth abscess requires prompt treatment, as the infection can spread into the bones of your jaw as well as other areas of your head and neck. In some cases, treatment may involve removing the affected tooth.

Stage 5: Abscess

As tooth decay advances into the pulp, bacteria can invade and cause an infection. Increased inflammation in the tooth can lead to a pocket of pus forming at the bottom of your tooth, called an abscess.
Tooth abscesses can cause severe pain that may radiate into the jaw. Other symptoms that may be present include swelling of the gums, face or jaw, fever, and swollen lymph nodes in your neck.

Figure 4

Matrix metaloprotienases:

MMPs are a group of enzymes in charge of the cleavage of the components that make up the ECM, which are involved in different physiological and pathological processes that occur in living tissues and can activate growth factors, within their immediate environment, cell surface receptors and adhesion molecules (Harbor Perspect. Biol. 2011). These metalloproteinases constitute an important family of zinc-dependent endopeptidases and their activity is regulated by specific inhibitors known as tissue inhibitors of metalloproteinases (TIMPs) (Harbor Perspect. Biol. 2011).

matrix metaloprotienases are classified according to their presumed target substrate specificity, structure and biofunctionality, into five main classes:
1-collagenases
2-gelatinases
3-stromelysins
4-matrilysins
5-membrane-type MMPs in addition to others.

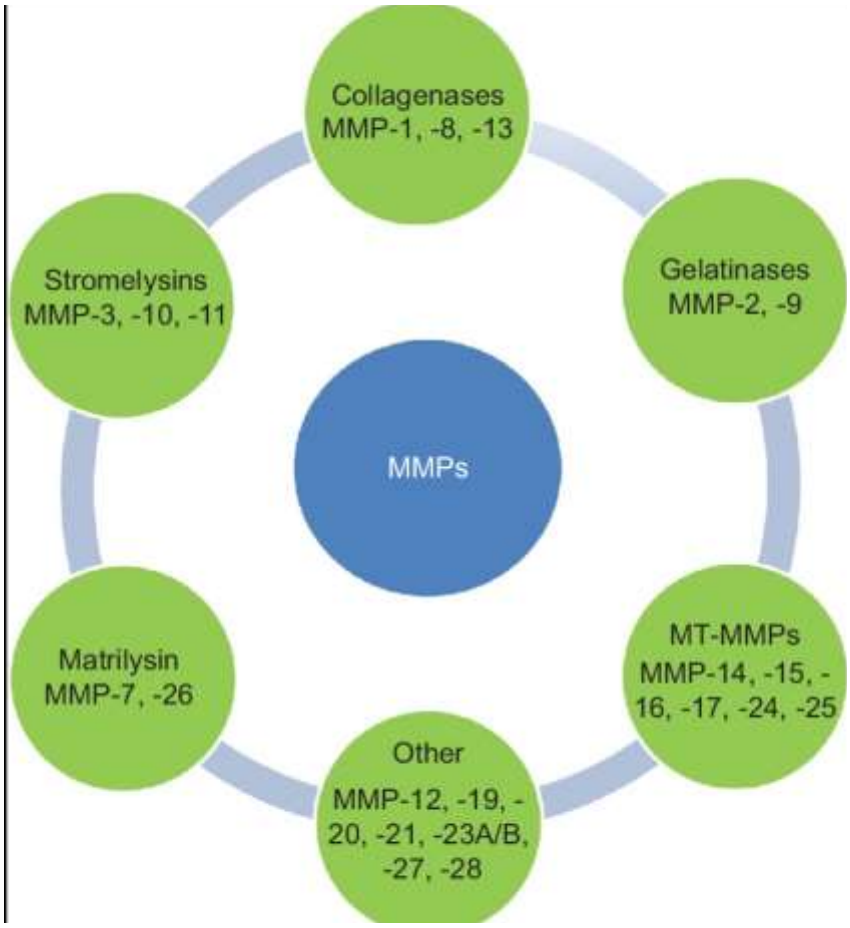

Figure 5

Matrix metaloprotienases and Dental Caries:

The accumulating cariogenic bacteria produce acids like lactic acid that reduce the local pH, leading first to the demineralization and later to the destruction of the organic matrix through the activation of endogenous MMPs in saliva, gingival fluid, and dentine [Deo, P.N.; Deshmukh, R.2019]. Caries progress as demineralization cycles prevail and remineralization cycles cease [Featherstone, J.D. Featherstone, J.D.2008]. Classically, bacterial proteases are blamed for the proteolytic process taking place because of dental caries. However, activated endogenous MMPs in dentine, gingival crevicular fluid and saliva, share in degrading the dentine matrix of demineralized dentine at neutralized pH levels. Collagen in the caries affected dentine retains the capability to remineralize until it is totally devoid of mineral nanocrystals [Mazzoni, et al R.;2015]. Bacterial collagenases in addition to endogenous MMPs of salivary, gingival fluid and dentinal origin share in the dentine matrix degradation process in active carious lesions. The endogenous dormant MMPs are activated by local pH changes indicating the contribution of bacterial acids. The comparatively higher levels of MMP-8 and -9 in the outer zones relative to the inner caries affected zones indicate the role of MMPs of salivary origin in the process.

MMPs currently known to participate in dental caries and dental restoration failure:

MMP-1 (collagenase-1)
MMP-2 and -9 (gelatinase-A and -B)
MMP-3 (stromolysin-1)
MMP-8 (collagenase-2)
MMP-20 (collagenase-3). [Allam, E.; Feitosa, S.;2015].

During the carious process, pro-MMPs become activated through acidic pH (4.5). Following their activation, MMPs become stable by pH neutralization due to the salivary buffering effect [Allam, E.2015].

During dental caries, MMPs develop proteolytic activity: MMP-20, MMP-2, -3, -9 and
-8 are detected in carious dentine in dormant and active forms.

In detail:

*MMP-1 and especially MMP-8 work as collagenases, the most powerful digesting type I collagen.
*MMP-2 and MMP-9 gelatinases, have the potential to disrupt the terminal of the collagen molecule.
However, while MMP-9 is identified in greater concentrations in deep levels of caries, MMP-2 has no variation regarding caries depth [Ballal, et all 2017].
*MMP-3 releases proteoglycans like decorin, followed by cytokines that potentiate degradation of the demineralized dentine matrix [Chaussain, et all 2013].
Cysteine cathepsin of dentine is able to activate latent MMPs. At increasing depth of carious lesion, cathepsin activity becomes stronger with greater collagenolytic potential as more MMPs become activated [Brodzikowska, et al, K.2019].
Regardless of the rate of progress of dental caries, endogenous dentine MMPs decrease with aging.

Activation of MMPs:

MMP activity in response to disease may arise from exogenous (bacterial products) and endogenous (immune cells) sources as well as from dentine matrix reservoirs. Bacterial products from carious lesions may also lead to signalling cascades that activate MMP secretion by odontoblasts. (Charadram et al., 2012) Their activation and interaction are regulated by certain extracellular matrix constituents as well as by TIMPs. Chemical interactions of signaling molecules, cytokines, growth factors or other MMP family members or by mechanical changes in the extracellular matrix can activate MMPs [Mazzoni, et all 2015].

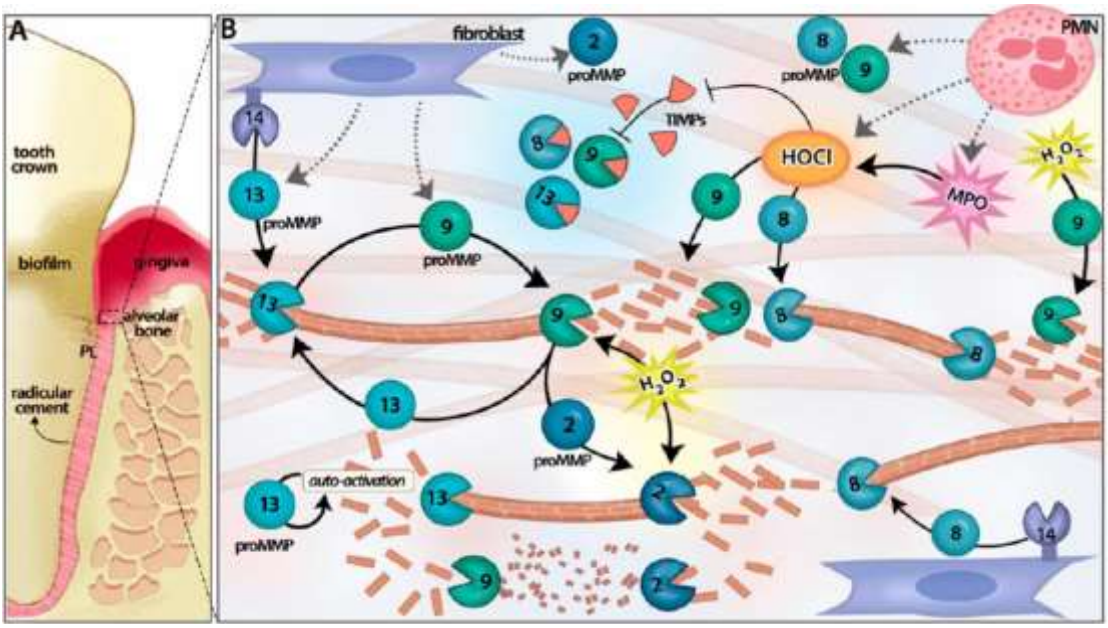

Figure 6

Matrix metaloprotienases in Pulpal and Periapical Lesions:

Odontoblasts and fibroblasts of the pulp can also express MMPs, especially MMP-13 and MMP-1 [Wahlgren, et al.20022]. In reversible and irreversible pulpitis, MMPs play a bifunctional role of tissue destruction and downgrading, together with tissue protection and mediation of host immune responses [Torres, et al2020]. During progression of caries, proteolytic cleavage of dentine matrix by: MMP-1, -3, -8, -9, -13 and more significantly MMP-20, can play a signaling inductive dentinogenesis for tertiary dentine formation and dentine-pulp wound healing [Okamoto, M.; et al .2018].

On the other hand, there is a more increased release of active MMPs in pulpitis than in healthy pulp tissue, indicating their role in pulp inflammation:

released cytokines (IL- 1β) and tumor necrosis factor-α (TNF-α) in pulp inflammation, activate MMP-1, MMP-2and TIMP1 gene expression [Brodzikowska, et al 2019].

While MMP-2 expression was observed in the dental papilla cells, dental follicle, ameloblasts, odontoblasts and bone cells from the coronal and basal regions of the bony crypt [Sandoval, N.G.; Nayra, S.L.; Bautz, W.G.2019]. bacteroids and anaerobic bacteria can also stimulate excretion of MMP-1, MMP-2 and TIMP1 by the pulp cells [Brodzikowska, A.; Gondek, A.2019]. The level of MMP-2 in root canal exudate of teeth with pulp necrosis or asymptomatic apical periodontitis is reduced gradually with root canal treatment procedures, which might validate MMP-2 as a biomarker.

Higher levels of MMP-8 are found in irreversible pulpitis with higher pain scores [58,59], explicitly expressed by polymorphonuclear leukocytes, macrophages, plasma cells and some endothelial cells of the blood vessels of the pulp tissue proper, suggesting the role of MMP-8 in extracellular matrix degradation during pulp and periapical tissue inflammation.

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The level of MMP-8 progressively decreases after 15 days of a mineral trioxide aggregate (MTA) pulpotomy procedure in rat molars, significantly more than Biodentine and calcium hydroxide pulpotomies, indicating the superiority of MTA for vital pulp therapy [Cunha, N.N.D.O.; Junqueira, M.A.2021].

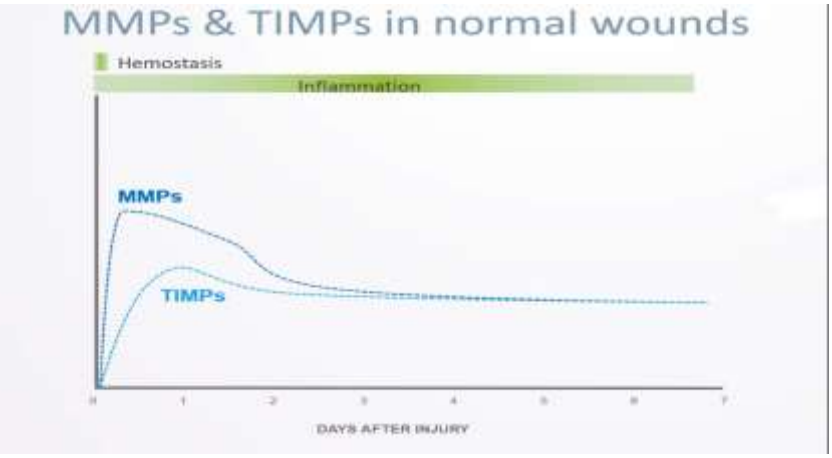
MMP-9 expression is enhanced in inflamed pulps, especially in endothelial cells, inflammatory infiltrate, odontoblasts, and fibroblasts [61]. In patients with symptomatic irreversible pulpitis treated with a single visit mineral trioxide aggregate pulpotomy, active MMP-9 concentration in pulpal blood has a significant correlation with the outcome, possibly indicating a prognostic biomarker,

In a recent clinical study, inflammatory cytokines and MMPs were assessed in collected dentinal fluid after selective caries removal and treating dentine with selfetching adhesives in patients with deep caries. They were used in immunoassays as biomarkers of inflammation to detect the influence of clinical procedures of selective caries removal and adhesive materials on the pulp tissue. Eight weeks following selective caries removal, MMP-8 and TIMP1 levels increase [Schmidt, et al .2021]. Bone resorption in apical periodontitis is linked to host inflammation and immune response. As osteoclasts start their bone resorption activity, MMPs such as MMP-9 should be functional since they contribute to degradation of the bone organic matrix. Biomarkers of bone resorption in apical periodontitis including MMP-9 in controlled diabetic and normoglycemic patients are not significantly different [Sarmento, et al .2020].
MMP-9 is reduced by sodium hypochlorite and sodium hypochlorite limewater. When an intracanal medication of calcium hydroxide and chlorohexidine is used, reduction in MMP-9 and MMP-8 levels is potentiated.

Matrix Metaloprotienases Inhibitors:

The evident role of MMPs in the pathogenesis and progress of dental caries has drawn the interest of researchers to stop dental caries, not only by combating cariogenic microorganisms, but also by developing inhibitors for endogenous MMPs in dentine and saliva in the form of gels and mouth washes and stop caries and promote healing and remineralization, Moreover, MMP inhibitors are suggested to resist dentine abrasion and erosion [Hannas, A.R.2016].

Figure 7



Matrix Metaloprotienases can be inhibited by endogenous and exogenous inhibitors:

Endogenous tissue inhibitors (TIMPs 1, 2, 3, 4) regulate and control MMP expression and function. Each TIMP has a specific gene regulation pattern, expression profile and binding affinity to specific MMPs [Sulkala, M.2004]. TIMPs are present in the ECM in a soluble form, except for TIMP-3, which is bound to the ECM. All TIMPs inhibit MMPs through reversible blockage forming 1:1 stoichiometric complexes [Benjamin, M.20122].

Both MMPs and TIMPs have important roles in the maintenance of health and disease and their abnormal regulation has a relevant role in pathological conditions. Therefore, MMPs and TIMPs could be important biomarkers of disease [Cabral-et al 2020].

For instance, increased levels of MMP-8 and the MMP-8: TIMP-1 ratio in saliva and serum seem to be more pronounced in women with polycystic ovarian syndrome and they are potentiated by gingival inflammation [Akcalı, et al 2015].
TIMP1 might have a role in dental pulp inflammation. Moreover, TIMP-1 is associated with acute apical periodontitis probably as a defense mechanism to avoid extensivedestruction [Letra, A.; Ghaneh, G.2013].
Accumulating evidence shows that both MMPs and TIMPs play a role in development, progress, and wound healing of apical periodontitis. However, more research is needed to elucidate the exact role of respective MMPs and TIMPs in the different stages of apical periodontitis and influences on severity of bone destruction and wound healing [Wan, et al 2021].
Exogenous inhibitors in dentistry include multiple synthetic and natural compounds that can protect dentine and prevent the demineralization process via inhibition of theproteolytic activities of MMPs:
*Chlorhexidine, fluorinated products, indomethacin, tetracyclines, sodium trimetaphosphate, stannous chloride benzalkonium chloride, alcohols like ethanol, quaternary ammonium compounds [Wan, et al 2021],
*as well as other crosslinking and medicinal plants like green tea, grape seed extracts and curcumin are famous examples. Animal studies show that certain chemicals with MMP inhibitors such as modified tetracycline and zoledronate, are effective in reducing dentine caries, which demonstrates the significance of MMPs in dental caries [Tian, Z.et al 2018].

An enzyme linked immunosorbent assay of dentinal fluid collected from both shallow and deep carious lesions found significant correlation between MMP-9 in shallow and deep caries. These findings indicate that individuals with more MMP-9 in deep caries are likely to have more MMP-9 in shallow caries. Higher levels of MMP-1 and -2 are found in the saliva of patients with caries rather than in healthy individuals. However, the levels of MMP-1 and -2 decrease after treatment.

Chlorhexidine:

Chlorhexidine is extensively used in dental clinics as an antimicrobial agent to treat gingivitis and periodontitis. In addition, it prevents dental plaque and can be used as an adjunct to mechanical debridement. It has been reported that 2% chlorhexidine gluconate is capable of preventing reduction in resin-dentin bond strengths. By binding to the zinc and calcium ions, in the catalytic domain of MMP, chlorhexidine is able to inhibit MMP activity.
*Chlorhexidine has marked effects as an exogenous inhibitor against matrix metalloproteases. It effectively and nonspecifically reduces collagen degradation by collagenolytic enzymes like MMPs and cysteine cathepsin [Scaffa, P.M.; et al 2012]. It also provides inhibitory effects against MMPs in acidic environments produced by acid etching and dental caries.
The controlled release of chlorohexidine at the dentine surface by adding clays to dentine bonding agents was found to improve durability of resin bonds to dentine [De Menezes, L.R.; da Silva, 2019].
Different studies and systematic reviews, indicate that chlorohexidine improves the longterm stability of resin bonds to dentine with some limitations concerning the test aging periods and the need for more supportive clinical data [Montagner.2014].
Osorio et al. also investigated whether the degradation of the dentine hybrid layer might be restricted by chlorhexidine digluconate following multiple demineralization techniques using phosphoric acid, EDTA or acidic monomers. They found that chlorhexidine has a partial inhibitory effect against MMPs in case of the acidic monomers, which was prolonged in comparison with phosphoric acid or EDTA. Notably, the inhibitory activity of chlorhexidine, at concentrations of 0.5%, 1.0% and 2.0%, against MMPs were maintained after treating dentine powder with two-step selfetching primers.

Fluorinated Products:

Fluorinated products are a useful tool in dentistry to prevent dental caries.
Studies showed that they have MMP inhibitory effects. It was suggested that fluoride, in the form of sodium fluoride, might prevent dental caries through inhibition of salivary and purified human gelatinases MMP-2 and MMP-9 [Kato, M.T.2014].
In contrast, it was reported that sodium fluoride might show low efficiency as a direct inhibitor of dentine matrix-bound matrix metalloproteinases [Brackett, M.G.2015].
Another study by the same research group demonstrated that potassium fluoride might inhibit the proteolytic properties of dentine matrix-bound cysteine cathepsins without a visible efficacy against dentine MMP activity [Altinci, P2019].
Treatment of dentine with sodium trimetaphosphate, a synthetic compound that reduces dentine demineralization, inhibited MMP-2 and MMP-9 activities particularly at 1.5% concentration [Gonçalves, R.S.2018].

Dentifrices that contain MMP inhibitors including:
*sodium fluoride
*green tea extract
*chlorhexidine digluconate
can markedly decrease dentine loss [49], preserve the surface properties of eroded dentine specimens and counteract dentine abrasions and erosions [Brodzikowska, A.2019].

Tetracyclines:

Tetracyclines have innate MMP inhibitory capacity.
Chemically modified tetracycline-3 showed preservative ability against the progression and prevalence of dentine caries in rats [Xu, J.; Miao, C.; Tian, Z.2018].
Inhibition of MMP activities using chemically modified tetracycline-3 lowered the organic bone matrix degradation in rats and resulted in reduced tooth movement [Ramamurthy, N.S.2002].

Doxycycline:

is indicated for use in periodontal disease and is the only collagenase inhibitor approved by the US Food and Drug Administration for any human disease [Vandenbroucke, R. E2014].
Oliveira et al., 2016 reported that pretreatment with doxycycline either as acidic or neutral solutions had no effect on bond strength of dentine adhesive [OliveiraHde, L.2016].

Moreover, encapsulated doxycycline, as a MMP inhibitor, might improve the durability and performance of hybrid layers in adhesively bonded resin used in restorative dentistry [Feitosa, S. A2014].
Inhibition of MMP activities using chemically modified tetracycline-3 lowered the organic bone matrix degradation in rats and resulted in reduced tooth movement [Ramamurthy, N.S.2002].

Discussion:

In 2003 Robert Visse and Hideaki Nagase Considerable advancements have been made in the understanding of biochemical and structural aspects of MMPs, including their activation and catalytic mechanisms, substrate specificity, and the mechanism of inhibition by TIMPs in addition, although collagenase was the first member of the family to be discovered, Currently, 23 MMPs are known in humans, but their biological functions are not clearly understood.

But in 2009, it is important to note the role of MMP-20 (enam- elysin) in the progression of caries. MMP-20 does not cleave Type I or Type II collagen as is evident from in vitro work Hence, this should be attributed to dentin bound MMP-20, which is host MMP. Dentin bound MMP-20 probably contributes to the early alteration in non-collagenous organic matrix during caries progression and in 2012Toledano found The dentin extracellular matrix can be compromised by proteolytic degradation, which happens in the presence of collagenases (MMP-1, MMP-8, MMP-13) and gelatinases (MMP-2, MMP-9).

In 2015 Atul Jain
Taking into consideration the enhanced presence of MMPs at the site of carious lesion, inflamed pulp and periapical tissue, together with the fact that when this inflammatory response subsides, the level of MMPs diminishes, it can be concluded that MMPs do play an important role in the degradation of the collagenous structure and spread of the pathology. At the same time, they are an essential component of the tissue in the physiologic process of tissue remodelling.

Recently studyin 2022 by Moataz et al, found MMP-1 (collagenase-1), MMP-2 and -9 (gelatinase-A and -B), MMP-3 (stromolysin-1), MMP-8 (collagenase-2) and MMP-20 (collagenase-3) are currently known to participate in dental caries and dental restoration failure.

In 2014 Kato, M.T. Found Fluorinated products are a useful tool in dentistry to prevent dental caries. Studies showed that they have MMP inhibitory effects. It was suggested that fluoride, in the form of sodium fluoride, might prevent dental caries through inhibition of salivary and purified human gelatinases MMP-2 and MMP-9.

In contrast, study by Brackett in 2015 it was reported that sodium fluoride might show low efficiency as a direct inhibitor of dentine matrix-bound matrix metalloproteinases Another study in 2019 by the same research group demonstrated that potassium fluoride might inhibit the proteolytic properties of dentine matrix-bound cysteine cathepsins without a visible efficacy against dentine MMP activity.

Concluding Remarks:

Understanding the role and biofunctional aspects of MMPs constitutes an integral part in figuring out the micromolecular basis of health and disease processes. This can open. the door for future paradigm shifts in diagnostic and therapeutic strategies. The active and dynamic participation of MMPs in developmental, degradational and pathological processes in dental tissues is increasingly drawing the attention of researchers. Research endeavors highlight the role of MMPs in the formative amelogenesis and dentinogenesis as well as in degradation of collagen in the hybrid layer, progress of dental caries, pulp and periapical inflammation, in addition to the healing of wounds of the dentine-pulp organ Ongoing research should continue to develop clinically effective MMP inhibitors with sustained potency to protect dentine matrix and provide adequate therapy for dentine caries, preserve the collagen hybrid layer, and maintain the longterm integrity of resindentine bonds, and facilitate remineralization, repair and regeneration of dental tissues. Moreover, future studies should continue to validate the suitability of using MMPs as diagnostic and prognostic biomarkers in dental caries, pulp, and periodontal lesions.

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

قالوا سبحانك لا علم لنا الا ما علمتنا انك انت العليم الحكيم

صدق الله العظيم