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Ich bedanke mich bei den unten aufgeführten Kolleginnen und Kollegen für ihre wertvolle Mitarbeit, die sie in den vergangenen zwei Jahren geleistet haben.

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The effects of matrix-metalloproteinases and chlorhexidine on the adhesive bond

A literature review

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endopeptidases,
hybrid layer,
collagen,
dentin

SUMMARY

The bond stability between dentin and filling material is the major challenge in modern adhesive techniques. A resin-dentin bond created by the etch-and-rinse technique considerably loses strength within 0.5 to 5 years. This may lead to secondary caries, hypersensitivity and finally loss of restorations. The decrease in bond strength is mainly due to two factors which are related to the collagen network of dentin and its constituent matrix-metalloproteinases (MMPs). Firstly, the collagen fibres exposed by the etching process using 37% phosphoric acid may not be completely infiltrated by subsequently applied adhesive bonding agents. In consequence, a thin layer of exposed, but non-infiltrated collagen remains at the bottom of the hybrid layer, resulting in nanoleakage. Secondly, this non-infiltrated collagen contains active MMPs that may degrade collagen by hydrolysis. Within dentin, these enzymes physiologically are inactive, but they become activated by phosphoric acid and acidic components of bonding agents. As a result, the hybrid layer disintegrates and the bond strength gradually diminishes. However, when chlorhexidine is used as a therapeutic primer following the etching process using 37% phosphoric acid, MMPs are inhibited in a non-specific manner, such that both the hybrid layer and the dentin bond strength are supposed to be preserved for a longer time period. Based on the studies included in this literature review, the use of a pure aqueous solution of 0.2% chlorhexidine as an additional therapeutic primer can be recommended for etch-and-rinse systems.

Introduction

The aim of the present study is to give an overview of the literature dealing with the effects of matrix-metalloproteinases (MMPs) and chlorhexidine on adhesive bond strength.

To this end, a literature search on the subject was performed in the PubMed databank. Search terms were "matrix-metalloproteinases" AND "chlorhexidine", "collagen" AND "matrix-metalloproteinases" AND "chlorhexidine", "bond strength" AND "chlorhexidine", "hybrid layer" AND "chlorhexidine", "matrix-metalloproteinases" AND "bond strength". Following an examination of the papers, the reference list was complemented using the search option "related citations". Publica-

tions which appeared in the period from 1962 (first description of the matrix-metalloproteinases by Gross & Lapière) to January 2013 were included in this survey.

Matrix-metalloproteinases

Matrix-metalloproteinases (MMPs) were first described in 1962 (Gross & Lapière 1962). These enzymes belong to the family of endopeptidases (Mazzoni et al. 2012, Thompson et al. 2012) and are localized in the extracellular matrix (Hannas et al. 2007, Kato et al. 2011, Osorio et al. 2011). Physiologically, MMPs participate in regular tissue remodeling by degrading proteins, with emphasis on collagen, via hydrolysis (Sorsa et al. 2004, Hannas et al. 2007, Osorio et al. 2011). For example, regular tissue remodeling takes place in the course of wound healing or angiogenesis (Hannas et al. 2007, Zhang & Kern 2009).

For the proper function of MMPs, metal ions (Ca^{2+}, Zn^{2+}) are essential (Breschi et al. 2007, Hannas et al. 2007, Tezvergil-Mutluay et al. 2010b). MMPs are almost ubiquitous in all body tissues and were found to be present in saliva, gingival crevicular fluid and dentin (Zhang & Kern 2009, Moon et al. 2010, Osorio et al. 2011). In dentin, the following of the altogether 23 human MMPs could be demonstrated: MMP-2, -3, -8, -9 and -20 (Tab. I) (Visse & Nagase 2003, Stanislawczuk et al. 2009, Mazzoni et al. 2012). These are produced by odontoblasts during dentinogenesis and subsequently incorporated into dentin in an inactive conformation (Kato et al. 2011, Mazzoni et al. 2011, Thompson et al. 2012). At acidic pH-values below 4.5, they are activated and become fully functional enzymes (Hannas et al. 2007, Moon et al. 2010, Kato et al. 2011).

As far as the dentin-pulp complex is concerned, it is currently assumed that MMPs are involved in the organization of the extracellular matrix prior to and during mineralization (Moon et al. 2010, Tersariol et al. 2010). Furthermore, they are supposed to play a role in the formation of peritubular dentin (Moon et al. 2010, Tersariol et al. 2010). Nevertheless, up to now little is known about the precise function of MMPs in mature dentin (Breschi et al. 2009).

MMPs and dental diseases

MMPs play a key role in many dental diseases. For instance, MMP-8 is known to be involved in periodontal diseases (Sorsa et al. 2004, Hannas et al. 2007, Zhang & Kern 2009) and MMP-20 takes part in the development of fluorosis and amelogenesis imperfecta (Hannas et al. 2007, Zhang & Kern 2009, Tersariol et al. 2010). In addition, MMPs are involved in the formation of erosions in dentin (Kato et al. 2010a, Kato et al. 2010b, Kato et al. 2011) as well as of dentin caries (Tjäderhane et al. 1998, Zhang & Kern 2009, Kato et al. 2011). In both processes, acids on the one hand lead to demineralization of dentin and consequently to exposure of collagen, while on the other hand they give rise to the activation of collagen-associated MMPs such that the exposed collagen is finally degraded by activated MMP. Hence, carious and erosive hard substance defects in dentin are developing following complete demineralization due to acidic activation of MMPs and subsequent collagen degradation. Accordingly, investigations demonstrated that MMP inhibition does not only prevent erosion development and progression, but seems to be even superior to fluorides (Kato et al. 2010a, Kato et al. 2010b) in terms of prevention of erosion.

Tab. I Matrix-metalloproteinases (MMPs) demonstrated in dentin

MMP-2	Gelatinase A
MMP-3	Stromelysin-1
MMP-8	Neutrophil collagenase/collagenase-2
MMP-9	Gelatinase B
MMP-20	Enamelysin

MMPs in adhesive techniques

Modern adhesive techniques are employed for both composite fillings and adhesive cementation of indirect restorations. The main issue in this process is the bond between hydrophilic dentin and hydrophobic composite, reported to considerably decline in strength and stability during the first 0.5-5 years (Zhang & Kern 2009, Pashley et al. 2010, Tezvergil-Mutluay et al. 2010c). One reason for this loss in bond strength is the hydrophilicity of the bonding agents, leading to the uptake of water and the elution of monomers. In addition, water uptake can give rise to hydrolytic degradation of monomers, i.e. dimethacrylates, by salivary esterases. Furthermore, bond strength is negatively affected by the dentinal fluid, which can also impair the bond of a composite to dentin (Breschi et al. 2007). Last but not least, an extreme sensitivitiy for handling issues of various adhesive systems hampers the creation of a stable bonding (Malacarne et al. 2006, Breschi et al. 2010, De Munck et al. 2010, Liu et al. 2011, Perdiago 2010, Tezvergil-Mutluay et al. 2010a, Mazzoni et al. 2012). Regarding MMPs, they affect the dentin-composite bond differently with respect to the adhesive system subtype, i.e. etch-and-rinse systems (acid-etch systems) and self-etch systems (self-etch or self-conditioning systems).

(a) Etch-and-rinse system

When using etch-and-rinse systems (acid-etch systems), dental enamel and dentin are demineralized by 37% phosphoric acid. As a consequence, the dentin collagen network is exposed, which ideally becomes completely infiltrated by the subsequently applied adhesive system, thusly forming the so-called hybrid layer (Breschi et al. 2007, Loguercio et al. 2009, Tersariol et al. 2010). However, remaining water in the collagen network and the chemical diffusion gradient of bonding agents prevent a thorough infiltration of the exposed collagen on a regular basis. At the bottom of the hybrid layer, there are always areas poor in bonding agent and rich in water, where non-infiltrated collagen is remaining (Breschi et al. 2007, Loguercio et al. 2009, Pashley et al. 2010).

This phenomenon was first described in 1995 by Sano et al. (1995a, b) and referred to as nanoleakage. In contrast to microleakage resulting from the formation of a gap (10-30 µm) *between* dentin and a non-adhesively fixed restoration material, nanoleakage results from a leak *within* the hybrid layer, without the formation of a gap between dentin and the restoration material. As a consequence, nanometer sized porosities (20-100 nm) are located in the basal part of the hybrid layer (Fig. 1) (Sano et al. 1995a, b, Sano 2006).

This aspect can be further worsened by too lengthy conditioning with phosphoric acid (Paul et al. 1999, Zhao et al. 2010) or by excessive drying of the dentin after the etching procedure (Kanca 1996, Ferrari & Tay 2003). Excessive drying makes the

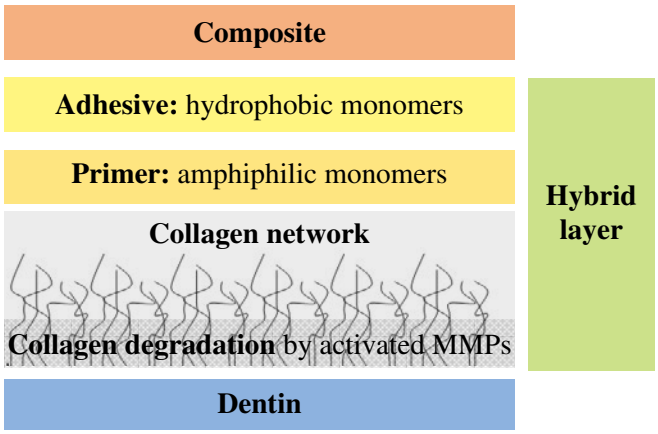

Fig. 1 Area of impact of MMPs on the bond between dentin and composite resin.

exposed collagen network collapse, which significantly impairs the penetration of the bonding agent and hence the formation of the hybrid layer (Kanca 1996, Ferrari & Tay 2003). Dentin overetching results in deeper demineralization and exposure of collagen. Hence, the bonding agent used thereafter may infiltrate the deep, basal layer of the collagen network less efficiently, thus enhancing nanoleakage (Paul et al. 1999, Zhao et al. 2010).

In this deep, basal layer of collagen that is not infiltrated by the bonding agent, existing MMPs are activated both by the applied phosphoric acid (pH=0.4) and by acidic monomers (pH=2–2.8) contained in the bonding agent (Breschi et al. 2007, Pashley et al. 2010, 2011, Mazzoni et al. 2011). However, there is evidence that the activity of MMPs is initially decreased by phosphoric acid, but they are subsequently re-activated by the bonding agent (Mazzoni et al. 2006, Sano 2006).

Consequently, exposed collagen is degraded by (re-)activated MMPs at the bottom of the hybrid layer, which gradually disintegrates due to growing and merging nanometer sized porosities (Fig. 1) (Sano 2006, Carrilho et al. 2007, Zhang & Kern 2009, Osorio et al. 2011, Mazzoni et al. 2012). Clinically, this degradation results in loss of retention or of fillings, secondary caries and hypersensitivity (Carrilho et al. 2007, Brackett et al. 2009, Loguercio et al. 2009, Moon et al. 2010).

Using *in situ* zymography, Mazzoni et al. (2012) provided direct evidence of active MMPs within the hybrid layer. For this purpose, histologic sections were incubated with specific proteins bound to exposed collagen which emit fluorescence signals upon degradation by MMPs. Using this approach, it was demonstrated that fluorescence exactly corresponded to the demineralized area (1–2 µm) at the bottom of the hybrid layer, which remained non-infiltrated by the bonding agent. Hence, in this area collagen degradation by MMPs verifiably took place (Mazzoni et al. 2012). The gradual disintegration of the hybrid layer *in vivo* was recorded by Carrilho et al. (2007) with the aid of transmission electron micrographs (TEM). After 14 months, TEM revealed a distinct reduction of hybrid layers (Carrilho et al. 2007).

Investigations using exogenous application of MMPs demonstrated that the latter did not result in enhanced disintegration of the hybrid layer. Hence, collagen degradation rather relies on endogenous MMPs than on additional exogenous enzymes from saliva (Carrilho et al. 2007, Toledano et al. 2007).

In order to prevent the hybrid layer degradation by MMPs, the goal of adhesive techniques must be either a complete infiltration of the collagen exposed by phosphoric acid or the inhibition of MMPs located in the demineralized area (Zhang & Kern 2009, Liu et al. 2011). For MMP inhibition, the use of chlorhexidine (CHX) (Fig. 2) as therapeutic primer has proved suitable, i.e. following the etching procedure with 37% phosphoric acid and prior to the application of the bonding agent (Hebling et al. 2005, Breschi et al. 2007, Carrilho et al. 2007, Loguercio et al. 2009, Moon et al. 2010, Pashley et al. 2010, Boushell et al. 2011, Osorio et al. 2011). CHX acts as unspecific inhibitor of MMPs by altering their three-dimensional structure and depleting metal ions (Ca^{2+}, Zn^{2+}), which are necessary for their function (Fig. 3b) (Loguercio et al. 2009, Moon et al. 2010, Osorio et al. 2011, Boushell et al. 2011). *In vitro,* CHX is able to inactivate all MMPs existing in dentin at a concentration of only 0.02% (Carrilho et al. 2007, Loguercio et al. 2009). Furthermore, CHX holds the advantage of a high substantivity (Loguercio et al. 2009, Carrilho et al. 2010, Liu et al. 2011). This term describes the chemical property of CHX to remain *in situ* due to its positive charge-related non-specific binding, and thus exert its influence beyond the mere duration of application. For this reason, it may be assumed that the concentration of CHX and the duration of its application are of minor importance (Carrilho et al. 2007, Breschi et al. 2009, Loguercio et al. 2009). Accordingly, recommendations of usage range from 2% CHX for 60 s (Carrilho et al. 2007, Breschi et al. 2009, Loguercio et al. 2009, Moon et al. 2010, Boushell & Swift 2011, Osorio et al. 2011) to 0.002% CHX for 15 s (Breschi et al. 2009, Loguercio et al. 2009). However, there is scientific unanimity with respect to the form of application: CHX should always be used as a pure aqueous solution, rather than in the form of conventional

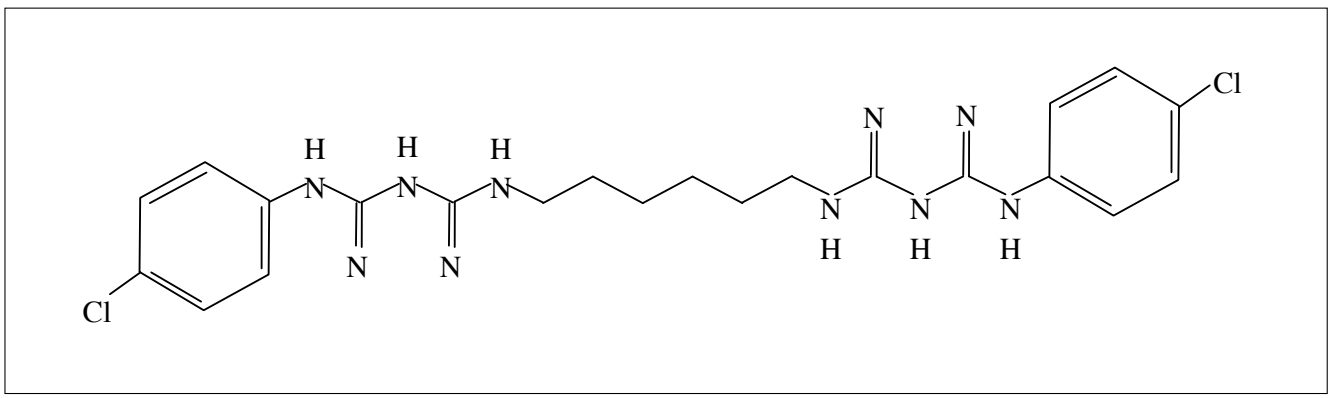

Fig. 2 Structural formula of chlorhexidine.

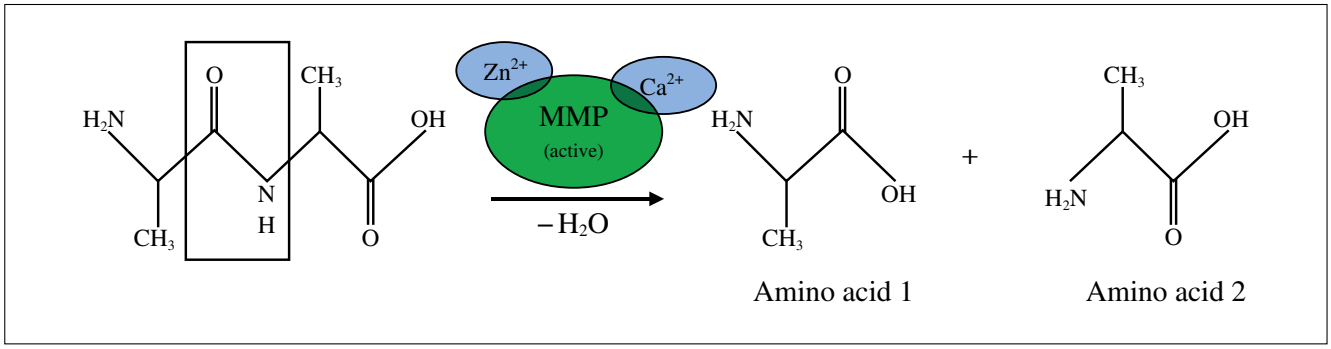

Fig. 3a Schematic representation of collagen degradation through cleavage of a peptide bond by matrix-metalloproteinases (MMPs).

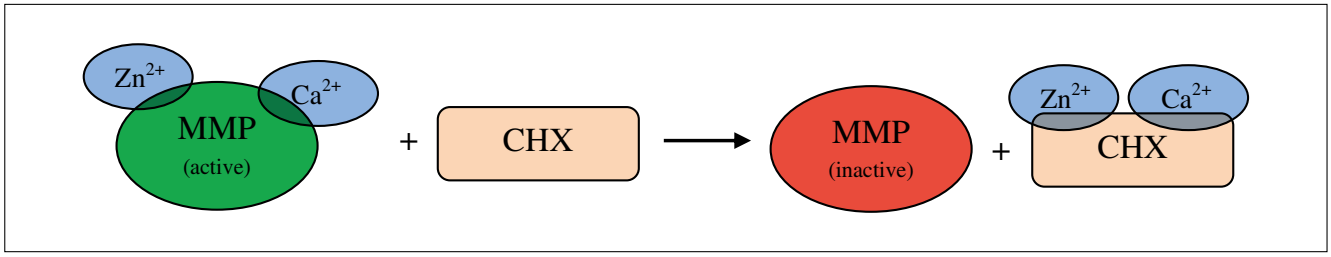

Fig. 3b Schematic representation of the effect of chlorhexidine (CHX) on MMPs: CHX depletes MMPs of the metal ions required for their function.

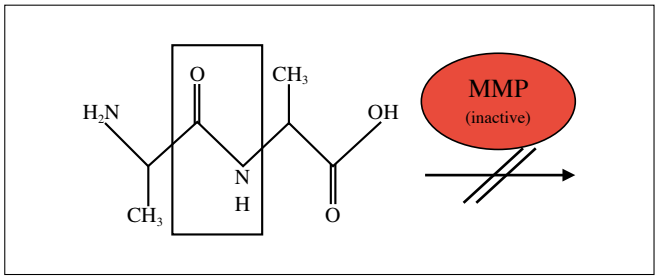

Fig. 3c MMPs inhibited by CHX are unable to cleave peptide bonds; hence no collagen degradation takes place.

mouthwash solutions, which potentially contain preservatives which may negatively affect the adhesive bond. Pure aqueous CHX solutions can be purchased or prepared by pharmacies.

Regarding CHX handling, it can be administered very easily with the aid of a foam pellet after the etching procedure and the thorough removal of the phosphoric acid. Following the appropriate exposure time, the cavity is air-dried and re-moistened with the selected adhesive system. Rinsing with water after CHX application should be avoided, because water can remove CHX from dentin (Carrilho et al. 2010, Kim et al. 2010). On the other hand, components of the bonding agent such as alcohol or HEMA do not dissolve CHX (Kim et al. 2010). Vice versa, CHX does not impair the properties of subsequently used bonding agents *in vitro* and *in vivo* and allows the formation of a regular hybrid layer (Carrilho et al. 2007, Brackett et al. 2007, Brackett et al. 2009, Loguercio et al. 2009, Moon et al. 2010). The immediate strength of the adhesive bond is not altered by CHX application, however, after longer periods of time, the stability of adhesive bonds created using CHX is even considerably improved (Brackett et al. 2007, Carrilho et al. 2007, Brackett et al. 2009, De Munck et al. 2009, Moon et al. 2010).

Thus, the application of CHX after the etching procedure both *in vitro* and *in vivo* results in a significantly diminished hybrid layer degradation, such that the adhesive bond to dentin is preserved for a longer time and nanoleakage is demonstrably decreased (Hebling et al. 2005, Brackett et al. 2007, Carrilho et al. 2007, Breschi et al. 2009, Loguercio et al. 2009). However, the maximum observation period so far was only two years (Moon et al. 2010). Little is known about how long CHX can maintain its inhibiting effect on MMP.

Meanwhile, there are attempts to integrate CHX in the phosphoric acid or the bonding agent (Stanislawczuk et al. 2009, Moon et al. 2010, Zhou et al. 2011). Such agents would hold the great advantage that no additional substance and no further work step is necessary for the creation of an adhesive bond. For example, an *in vitro* investigation (Stanislawczuk et al. 2009) showed that the incorporation of 2% CHX in 37% phosphoric acid results in findings similar to those obtained with the use of CHX as therapeutic primer. In both ways of CHX application, the adhesive bond to dentin remained stable for the first six months, whereas in control samples devoid of CHX, signs of disintegration of the hybrid layer were already recognizable. In the USA, phosphoric acid containing an integrated synthetic MMP-inhibitor (benzalkonium chloride, BAC) is already commercially available (Bisco, Schaumburg, USA) (Tezvergil-Mutluay et al. 2010c, Thompson et al. 2012).

Although the activity of MMPs in dentin powder was reduced in the presence of CHX incorporated in primers and adhesives, there are so far no data on adhesive bonds to dentin having been created using these modified adhesive systems (De Munck et al. 2009, Almahdy et al. 2012). An investigation on primers containing synthetic MMP-inhibitors (batimastat and galardin) revealed that the adhesive bonds to dentin were similar to or worse than those obtained using conventional primers (De Munck et al. 2009, Almahdy et al. 2012).

Apart from experiments with CHX, there are also attempts to inactivate MMPs with the aid of galardin (Breschi et al. 2010, Tezvergil-Mutluay et al. 2013). This is a synthetically manufactured, specific MMP-inhibitor. Similar to CHX, galardin is ap-

plied as additional primer after the etching procedure and does not seem to affect the properties of subsequently used bonding agents. A possible advantage compared to CHX could be that based on its specific action, galardin exerts its inhibiting effect at much lower concentrations of 0.2 mM (Breschi et al. 2010, Tezvergil-Mutluay et al. 2013).

(b) Self-etch systems

Self-etch systems, i.e. self-etch and self-conditioning systems, are less susceptible to handling issues than etch-and-rinse systems, but are inferior to these with respect to adhesive bond strength, restoration margins quality, and long-term stability (Inoue et al. 2001, Van Meerbeek et al. 2003).

In self-etch systems, dentin etching, collagen exposure and infiltration of the exposed collagen are accomplished simultaneously (Van Meerbeek et al. 2003, Carvalho et al. 2005, De Munck et al. 2010, Pashley et al. 2010). As a result, less exposed collagen exists underneath the hybrid layer, because there is no difference in penetration depth between the acid and the priming monomers. Thus at a first glance, there seem to exist less problems related to nanoleakage for self-etch than for etch-and-rinse systems. However, a study of Carvalho et al. (2005) examining ten self-conditioning adhesive systems showed that nanoleakage can also occur in self-conditioning systems using weak acids.

In contrast to etch-and-rinse systems, self-conditioning systems usually contain more hydrophilic monomers, yielding an increased permeability of the hybrid layer for water and leading to an enhanced monomer elution (Breschi et al. 2007, Liu et al. 2011). Hence, also for self-etch systems there is exposed collagen which can be degraded hydrolytically by potentially activated MMPs. In the literature, inconsistent data exist regarding the question whether self-conditioning systems enhance the activity of MMPs in dentin (-powder) (Nishitani et al. 2006, De Munck et al. 2009, Lehmann et al. 2009, De Munck et al. 2010, Liu et al. 2011, Zhou et al. 2011).

In self-conditioning systems, only the integration of MMP inhibitors in the bonding agent would permit an effective inhibition of MMP. However, the incorporation of CHX (0.05%) in a self-etching primer could not prevent a decrease (over 12 months) of the adhesive bond (De Munck et al. 2009). Furthermore it has been demonstrated that CHX integration in self-conditioning systems can impair the mechanical properties of the bonding agents and the adhesive bond to dentin (Liu et al. 2011).

Thus, up to now it has not yet been clarified conclusively to which extent MMPs play a role in self-conditioning systems.

Other endopeptidases: cysteine cathepsins

The hybrid layer and hence the adhesive bond strength between tooth and composite resin is further affected by a group of enzymes apart from MMPs, namely cysteine cathepsins, which are endopeptidases being produced by various cell types, including odontoblasts and pulpal tissue cells. Cysteine cathepsins hydrolytically degrade the extracellular matrix, in particular collagen, and, similar to MMPs, they seem to be involved in the degradation of exposed collagen at the bottom of the hybrid layer (Tersariol et al. 2010, Liu et al. 2011, Scaffa et al. 2012, Tezvergil-Mutluay et al. 2013, Tjäderhane et al. 2013).

E-64 is an epoxy which is able to irreversibly inhibit cathepsins and therefore acts as specific inhibitor of cysteine cathepsins (Tezvergil-Mutluay et al. 2013). However, studies showed that CHX due to its unspecific activity does not only inactivate MMPs, but also cysteine cathepsins (Tezvergil-Mutluay et al. 2013). Therefore, CHX as primer further holds the advantage of avoiding the necessity for an extra inhibitor of cysteine cathepsins.

Perspective

Apart from CHX, additional inhibitors of MMPs are investigated, for example EDTA (ethylenediaminetetraacetic acid) (Thompson et al. 2012), BAC (benzalkonium chloride) (Tezvergil-Mutluay et al. 2010c), PVPA (polyvinylphosphonic acid) (Tezvergil-Mutluay et al. 2010a) and galardin (Breschi et al. 2010, Tezvergil-Mutluay et al. 2013). Other new concepts for the stabilization of the hybrid layer deal, amongst others, with electrically assisted infiltration of the bonding agent (Liu et al. 2011). This concept aims at reducing the discrepancy between the penetration depth of the phosphoric acid and the diffusion depth of the bonding agent. Moreover, there are promising approaches using crosslinking substances, which are intended to stabilize the exposed collagen network in order to render it more resistant to the degradation by MMP (Liu et al. 2011).

Conclusion

The adhesive bond to dentin declines within the first 0.5–5 years. Involved in this phenomenon are, among other things, matrix-metalloproteinases (MMPs), which degrade collagen that is not infiltrated by bonding agents at the bottom of the hybrid layer. Using chlorhexidine (CHX) as therapeutic primer in etch-and-rinse systems, these enzymes are inhibited and the adhesive bond to dentin is maintained for a longer time period.

Apart from MMPs, other factors also affect the adhesive bond quality such that it usually diminishes gradually to some degree. However, due to MMP inactivation by CHX, it remains stable for longer periods (Carrilho et al. 2007, De Munck et al. 2009, Breschi et al. 2010, Liu et al. 2011). The utilization of CHX is not able to completely prevent nanoleakage and subsequent gradual loss of the adhesive bond, but it is certainly an important step towards a durable and stable adhesion between dentin and composite resin.

In summary, when using etch-and-rinse systems, applying a pure aqueous solution of CHX (0.2%; 30 s) as therapeutic primer *after* etching and *before* administration of the bonding agent can contribute to a delay of degradation processes and hence improves the long-term stability of the adhesive bond to dentin.

Résumé

Dans le cadre des techniques adhésives modernes, l'interface connective entre la dentine et la résine (composit) constitue encore un défi majeur. Au cours des premiers 0,5 à 5 ans, le lien de la dentine avec la résine, créé par l'intermédiaire de la technique décapante-rinçante, perd clairement de sa solidité; ceci peut engendrer de la carie secondaire, de l'hypersensibilité et la perte des obturations. La réduction (de la stabilité) du lien adhésif est suscitée par deux éléments principaux: le collagène et ses métalloprotéinases matricielles (MMPs). D'abord, le collagène, qui a été déroché par décapage de la dentine avec l'acide phosphorique (37%), n'arrive pas à être infiltré complètement par le promoteur d'adhérence. La conséquence est une nanofuite («nanoleakage»), c'est-à-dire une couche de collagène déroché entre la couche hybride et la dentine. Le collagène non infiltré contient en plus des MMPs, qui peuvent hydrolyser la

matière organique. D'habitude, ces enzymes existent dans un état inactif, mais elles sont activées par l'acide phosphorique et le promoteur d'adhérence. C'est ainsi que la couche hybride est peu à peu désintégrée et perd son lien adhésif avec la dentine. Il existe une possibilité d'empêcher ce processus en inhibant l'activité des MMPs avec de la chlorhexidine. Lors de l'emploi de la chlorhexidine comme amorce thérapeutique après le décapage avec l'acide phosphorique (37%), les enzymes sont inhibées de manière non spécifique. La couche hybride et le lien adhésif entre la dentine et la résine restent ainsi conservés plus longtemps. En résumé, l'utilisation de la chlorhexidine (0,2%) comme amorce thérapeutique additionnelle est recommandée lors de l'emploi des systèmes décapants-rinçants.

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