UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

FRANCIELLY DA SILVA CAMIM

Influence of MMP inhibitors on bond strength of adhesive restorations: systematic review and meta-analysis

A influência de inibidores de MMP na resistência de união de restaurações adesivas: revisão sistemática e metanálise

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“Nada é tão nosso quanto nossos sonhos”

Friedrich Nietzsche

ABSTRACT

Influence of MMP inhibitors on bond strength of adhesive restorations: systematic review and meta-analysis

Objectives: This systematic review aimed to evaluate the effect of metalloproteinase (MMPs) inhibitors on bond strength using initial (24 hours) and long-term (6, 12 months or longer) microtensile tests.

Sources: A search was carried out in 7 databases and in the gray literature, limited to Portuguese, English and Spanish languages without publication year limit, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) 2009.

Study selection: Only *in vitro* studies assessing the use of MMP inhibitors in adhesive procedures were included. Meta-analyses were conducted with the extracted data and the studies were evaluated for the risk of bias.

Data: Of 5,134 potentially eligible studies, 112 were selected for full-text reading, 48 were reviewed, and 43 were included in the meta-analysis. Two independent evaluators selected the studies and assessed the risk of bias. Estimates of the combined effect were reported as means and standard deviation between groups. The most commonly used MMP inhibitor was chlorhexidine (CHX). The initial values of bond strength were higher when CHX was used ($p < 0.05$), but no difference was found in the other time-points between groups using inhibitors and control groups. Etch-and-rinse adhesive systems presented better results with the use of CHX, which was not seen in self-etching systems. None of the included studies had low risk of bias, but the analysis including only studies of medium risk of bias showed similar results to the analysis with studies of high risk of bias.

Conclusion: The use of 2% CHX affected positively the initial bond strength, but no inhibitor was effective in maintaining the bond strength after the aging process.

Key words: Matrix Metalloproteinases. Dental bonding. Protease Inhibitors

RESUMO

A influência de inibidores de MMP na resistência de união de restaurações adesivas: revisão sistemática e metanálise

Objetivo: O objetivo deste estudo foi revisar sistematicamente a literatura em busca de estudos in vitro que avaliaram a influência da utilização de inibidores de metaloproteinase (MMP) durante procedimentos adesivos na resistência de união por meio de testes de microtração iniciais (até 24 horas) e a longo prazo (6 e 12 meses ou mais). **Fontes:** A busca foi realizada em 7 bases de dados e na literatura cinza, limitado às línguas portuguesa, inglesa e espanhola sem limite ano de publicação, seguindo a declaração Preferred Reporting Items for Systematic Reviews e Meta-Analyzes (PRISMA) 2009. **Seleção dos estudos:** Apenas estudos in vitro sobre o uso de inibidores de metaloproteinase em procedimentos adesivos foram incluídos. Metanálise foram conduzidas dos dados extraídos e os estudos foram avaliados para o risco de viés. **Dados:** De 5.134 estudos potencialmente elegíveis, 112 foram selecionados para análise de texto completo, e 48 foram incluídos para revisão, com 43 considerados na metanálise. Dois avaliadores independentes selecionaram os estudos e avaliaram o risco de viés dos estudos incluídos. As estimativas do efeito conjunto foram expressas como a valores brutos de média e desvio-padrão entre os grupos. O inibidor de MMP mais utilizado foi a clorexidina (CHX). Os resultados imediatos mostram maiores valores de resistência de união quando a CHX foi utilizada ($p<0.05$), os demais tempos estudados não evidenciam superioridade de nenhum dos inibidores estudados em relação ao grupo controle. Análises de modo de aplicação mostram que sistemas adesivos convencionais são beneficiados quanto ao uso de CHX, o que não acontece com os sistemas autocondicionantes. Nenhum estudo incluído se mostrou com baixo risco de viés, porém uma análise incluindo apenas estudos de médio risco de viés mostrou resultados semelhantes a análise cujo estudos de alto índice de viés foram incluídos. **Conclusão:** O uso de CHX afetou positivamente a resistência de união imediata, mas nenhum inibidor estudado se mostrou efetivo na manutenção da resistência de união após envelhecimento.

Palavras-chave: Metaloproteinases da Matriz. Colagem Dentária. Inibidores de Proteases.

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LIST DE ABBREVIATIONS AND ACRONYMS

MMP	Matrix metalloproteinase
CHX	Chlorhexidine Digluconate
Ca	Calcium
Zn	Zinc
PRISMA	Preferred Reporting Items for Systematic Reviews e Meta-Analyzes
PA	Proanthocyanidin
GD	Glutaraldehyde
EGCG	Epigalocatequina-3-galato
Y	Yes
N	No
Vs	Versus
EDC	Carbodiimide
TR	Randomization of teeth
TFCR	Caries-free teeth or restorations
MUAMI	Materials used according to the manufacturer's instructions
APSP	Adhesive procedure performed by a single operator
SZC	Calculation of sample size
BOTM	Blinding operator's test machine

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1 INTRODUCTION

1 INTRODUCTION

In 1955 Buonocore[1] took the first step to obtain restorations with micromechanical retentions to the dental structure by conditioning the dental enamel with 85% phosphoric acid. However, the development of methods that promote good adhesion in dentin was a more arduous assignment for the researchers, since this structure presents great tissue complexity, with great amount of organic matter and water in its composition[2]. Only in 1982, Nakabayashi et al.[3] demonstrated adhesion to the dentin substrate by infiltration of resinous monomers containing hydrophilic groups and subsequent polymerization in demineralized dentin, forming what is now known as the hybrid layer.

Dentin is a mineralized tissue that comprises a large part of the dental structure[4]. Its composed of 50% of inorganic material characterized by hydroxyapatite, 30% of organic matter, mainly type I collagen and 20% water[4]. The phosphoric acid conditioning removes the superficial mineral content (3 to 8μm) during adhesive procedures, exposing the collagen fibrils, which are infiltrated by hydrophilic resinous monomers with subsequent polymerization, thus forming the hybrid layer[2]. Nevertheless, resinous monomers are not capable of completely infiltrate dentin demineralized, leaving collagen fibrils exposed to degradation[5-7]. This degradation occurs mainly by the action of the endogenous metalloproteinases present in the dentin, particularly MMP-2, MMP-8 and MMP-9[8,9].

Moreover, a hydrolytic degradation phenomenon occurs in the hybrid layer due to the presence of residual water, capable of plasticizing the polymers causing cracks in the interface, liquid movement inside the hybrid layer and consequent loss of bond strength[10]. Similarly, these decrease in bond strength result in defects in demineralized dentin at the bottom of the hybrid layer[5,11].

Due to several studies on hybrid layer degradation researchers have seek alternatives to increase the longevity of adhesive interfaces[12-14]. Among them, the use of metalloproteinases inhibitors in dentin pretreatment, previously the infiltration of resinous monomers or after the application of acidified primers of the self-etching systems[15]. These studies showed the ability of metalloproteinase inhibitors to preserve

the bond strength when compared to untreated groups, especially when interfaces were aged either *in vitro* or *ex vivo*[8,14-17].

Among the inhibitors of metalloproteinases, the most widespread and studied substance is chlorhexidine digluconate, a potent synthetic antimicrobial agent that has been found to be an excellent inhibitor of endogenous enzymes of the dentin matrix. Several studies prove its effectiveness, showing a valuable alternative to delay the enzymatic degradation of adhesive restorations[8,113,114,18-22].

Even with the successful use of chlorhexidine, this substance shows a reversible mechanism and this occurs due to the leaching of this substance through the interfaces, thus reducing its inhibitory potential[18,23]. This fact led to the search for alternatives to chlorhexidine as the use of natural substances such as proanthocyanidin (PA), green tea extract and epigalocatequina-3-galato (EGCG) [24,25,28]. They can be found mainly in extracts of grape seed and cocoa, showing effectiveness in its use, but dependent on concentration and time of application[24-31]. Besides that other substances such as carbodiimide (EDC), glutaraldehyde (GD), galardin and riboflavin have been developed with the aim of inactivating the enzymes that cause degradation of the hybrid layer [24,31] .

In summary, many evidences can be found in the literature on the use of MMP inhibitors, both synthetic or natural[13-28,31] in preserve bond strength values when compared to control groups, without application of MMP inhibitor. Several inhibitors have already been tested but it is still unclear which would be the best option for clinical application, and whether these inhibitors would actually be effective. Therefore, the objective of this study was to systematically review the literature in search of *in vitro* studies comparing the use of metalloproteinase inhibitors compared to groups without the application of inhibitors on bond strength to dental structure through microtrensile bond strength test in dentin specimens evaluated initially or aged.

2 ARTICLE

2 ARTICLE

The article presented in this Dissertation was written according to the Journal of Dentistry instructions and guidelines for article submission

Influence of MMP inhibitors on bond strength of adhesive restorations: systematic review and meta-analysis

Short title: MMP inhibitors on bond strength: systematic review and meta-analysis

Francielly da Silva Camim[a]

[a]Department of Operative Dentistry, Endodontics and Dental Materials, Bauru School of Dentistry, University of São Paulo. Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP, Brazil/Zip Code:17012-901

fran.camim@hotmail.com

MS Student

Daniella Cristo Santin[a]

[a]Department of Operative Dentistry, Endodontics and Dental Materials, Bauru School of Dentistry, University of São Paulo.Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP, Brazil/Zip Code:17012-901

daniela_santim@hotmail.com

MS Student

Rafael Francisco Lia Mondelli[a]

[a]Department of Operative Dentistry, Endodontics and Dental Materials, Bauru School of Dentistry, University of São Paulo.Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP, Brazil/Zip Code:17012-901

rafamond@fob.usp.br

Full Professor

Linda Wang[a]

[a]Department of Operative Dentistry, Endodontics and Dental Materials, Bauru School

of Dentistry, University of São Paulo.Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP, Brazil/Zip Code:17012-901

wang.linda@usp.br

Full Professor

Heitor Marques Honório[b]

[b]Department of Pediatric Dentistry, Orthodontics and Collective Health, Bauru School

of Dentistry, University of São Paulo. Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP, Brazil/Zip Code:17012-901

heitorhonorio@usp.br

Associate Professor

Corresponding author: Prof. Dr. Heitor Marques Honório

Department of Pediatric Dentistry, Orthodontics and Collective Health, Bauru School

of Dentistry, University of São Paulo.

Alameda Octávio Pinheiro Brisolla, 9-75, Bauru, SP, Brazil/17012-901

Phone: +55-14-32266001/ +55-14-32358256

Fax: +55-14-3235-8323

E-mail: heitorhonorio@usp.br

Key words: matrix metalloproteinases, dental bonding, systematic review, meta-analysis, time factors, protease inhibitor.

ABSTRACT

Objectives: This systematic review with meta-analysis aimed to evaluate the effect of metalloproteinase (MMPs) inhibitors on *in vitro* bond strength using initial (24 hours) and long-term (6, 12 months or longer) microtensile tests.

Sources: A search was carried out in 7 databases and in the gray literature, limited to Portuguese, English and Spanish languages without publication year limit, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) 2009.

Study selection: Only *in vitro* studies assessing the use of MMP inhibitors in adhesive procedures were included (Kappa = 0.86). Meta-analyses were conducted with the extracted data and the studies were evaluated for quality. *Data*: Of 5,134 potentially eligible studies, 112 were selected for full-text reading, 48 were reviewed, and 43 were included in the meta-analysis. Two independent evaluators selected the studies and assessed the risk of bias. Estimates of the combined effect were reported as means and standard deviation between groups. The most commonly used MMP inhibitor was chlorhexidine (CHX). The initial values of bond strength were higher when CHX was used ($p < 0.05$), but no difference was found in the other time-points between groups using inhibitors and control groups. Etch-and-rinse adhesive systems presented better results with the use of CHX, which was not seen in self-etching systems. None of the included studies had low risk of bias, but the analysis including only studies of medium risk of bias showed similar results to the analysis with studies of high risk of bias. *Conclusion:* The use of 2% CHX affected positively the initial bond strength, but no inhibitor was effective in maintaining the bond strength after the aging process.

Clinical significance: The use of MMP inhibitors during adhesive procedures to promote greater longevity to adhesive restorations is controversial. This study contributes to the understanding of the influence of these inhibitors in bond strength of restorations, which may aid clinical applicability.

Key words: dentin bonding agents; enzymes inhibitors; matrix metalloproteinases; systematic review; meta-analysis.

INTRODUCTION

Since it was first reported by Nakabayashi et al. [1], resin adhesion to the dentin substrate has been the target of several studies [2,3]. During the adhesion process, a hybrid layer is formed by the infiltration of resinous monomers into the network of collagen fibrils that are exposed by acid etching and the removal of minerals [4]. The maintenance of a stable hybrid layer over time could promote greater longevity of the resin / dentin bond, and thus, greater effectiveness of the restoration [5].

However, the bond between resin and dentin is not stable and suffers significant loss of strength with aging [6-8]; it is believed that this loss is related to the degradation of the hybrid layer [9]. The two main mechanisms reported are the degradation of the collagen matrix by the action of endogenous metalloproteinases (MMPs) present in dentin [10] or the hydrolytic degradation of the resinous polymers that make up the hybrid layer [11,12].

The main endogenous MMPs of dentin are collagenase-2 (MMP-8), gelatinase-B (MMP-9) [13,14], and gelatinase-A (MMP-2) [13,14], which belong to the family of calcium and zinc-dependent proteolytic enzymes [15] found most frequently in dentin tissue affected by caries [15,16]. In its latent form, these MMPs are not able to degrade collagen; however, after the pH decrease during acid conditioning this MMPs is activated and followed by neutralization are able causing degradation of exposed collagen fibrils [15,17]. Thus, exposed collagen fibrils lead to decreased bond strength and cohesive failures in demineralized dentin below the hybrid layer, both in etch-and-rinse and self-etching adhesives [18,19].

Consequently, the inhibition of collagen degradation by MMPs would be beneficial to the hybrid layer [20]. Thus, antiproteolytic substances have been proposed to inhibit the action of MMPs and promote greater longevity of the adhesive bonds, such as the solutions applied in demineralized dentin prior to the application of adhesive systems [6,21-23].Several inhibitory agents have been studied, including chlorhexidine digluconate (CHX) solutions [6,7,21,24,25], proanthocyanidin (PA) [26-28], glutaraldehyde (GD) [26,28], epigallocatechin-3-gallate (EGCG) [29], galardin [30], green tea extract [30,31], among others. However, a large number of studies show favorable results regarding the use of these inhibitors [6,21,29,32] and others present unfavorable results [30,33], tested soon after application [34-38] or after an aging process [7,33,35-37,39].

In 2014, Montagner et al. [40] conducted a systematic review with meta-analysis at use of metalloproteinase inhibitor solutions, mainly emphasizing the influence of the use of CHX initial and after aging by means of bond strength tests. Differently from the Montagner study,

this study conducted meta-analyzes covering different MMP inhibitors, since several inhibitors can be found in the literature.

Therefore, the objective of this study was to evaluate the effect of specific or non-specific MMP inhibitors applied to dentin after acid etching for a etch-and-rinse adhesive system or after the application of the acidulated primer of self-etching systems, through a systematic review and meta-analysis. Microtensile tests were performed soon after the application and after the aging process. For the PICO structure was: P (patient- adapted for *in vitro* studies) - healthy dentin, I (intervention) – use of different MMP inhibitors; C (control) - without MMP inhibitors; and O (outcome) - bond strength by microtensile test. The key question guiding this review was: "What is the effect of specific or non-specific MMP inhibitors in the initial or long-term bond strength between resin and dentin, assessed by microtensile tests, compared to control." The null hypothesis tested was that the use of MMP inhibitors does not affect initial and long-term resin/dentin bond strength.

MATERIAL AND METHODS

Search strategies

This systematic review was based on the PRISMA strategy (Preferred Reporting Items for Systematic Reviews and Meta-Analyze) 2009 [41]. The best scientific evidence for studies aimed at verifying bond strength is provided by laboratory studies using microtensile tests. Randomized clinical trials and in vivo studies do not allow this type of analysis with exact numerical values. Therefore, this review aimed at in vitro studies that carried out microtensile test in dentin. For the PICO structure was adapted as follows: P (patient) - healthy dentin, I (intervention) – use of different MMP inhibitors; C (control) - without MMP inhibitors; and O (outcome) - bond strength by microtensile test. The key question guiding this review was: "What is the effect of specific or non-specific MMP inhibitors in the initial or long-term bond strength between resin and dentin, assessed by microtensile tests, compared to control."

Registration and protocol

This study was registered in the PROSPERO base (International prospective register of systematic reviews) with ID CRD42017077516, obtained when the protocol was sent to https://www.crd.york.ac.uk/prospero/.

Search strategy

An electronic search in the major scientific databases (PubMed, Web of Science, Scielo, Lilacs, Cochrane, Embase and Scopus) and in the gray literature BDTD (http://bdtd.ibict.br/vufind/) was performed based on the eligibility criteria. Languages were limited to English, Spanish, and Portuguese. Studies were included until January 29, 2018. The search strategy defined for the PubMed database was as follows: (((dentin*[tw] OR adhesi*[tw] OR ("dentin-bonding agents" OR "dental bonding" [MeSH Terms] OR (metalloproteinase* OR "metalloproteinase" OR "metalloproteinase" OR "metalloproteinase" OR "metalloprotease" OR "metalloprotease" OR protease "OR" metallo proteases "OR metalloprotease* OR mmp[tw] OR mmps[tw] OR protease* [tw] OR proteinase* [tw] [tw] OR storage* [tw] OR time factor*[tw] OR aging[tw] OR longevity[tw])). The strategy was adapted for the other databases.

Eligibility criteria

The inclusion criteria were in vitro studies that evaluated the influence of specific or non-specific MMP inhibitors applied to human or bovine (sound) dentin after acid etching, prior to the application of a etch-and-rinse adhesive system or prior to the application of primer in self-etching systems (external application) that were tested for adhesive strength (microtensile) at 24 hours after application or after an aging process (6 months or longer). Only studies that had a control group (without application of MMP inhibitors) submitted to the same aging conditions as the other test groups were included. Once the adhesive interface is being evaluated, studies evaluating resin cements by microtensile tests were also included. The test of microtensile is a technique is ideal for evaluating the long-term durability of resin interfaces once this technique produce better stress distribution at the true interface.

The authors of studies that did not provide the complete numerical data were contacted as an attempt to obtain the missing data and if the data were not provided the study was excluded. Studies that did not present a control group were excluded. Studies that applied the inhibitor prior to acid conditioning or in which the inhibitor was incorporated into the adhesive system or phosphoric acid were also excluded or only the data of interest were collected. Descriptive studies about MMP inhibitors were not used for quantitative purposes, but were included for the qualitative analysis of this review. In addition, studies that used carious, clarified, eroded, or divided dentin were excluded. A single study could be included more than once in the quantitative analysis if it reported results for different types of inhibitors, as in studies that studied more than one type of inhibitor.

Screening and selection

The collected data were inserted into the reference management software Endnote Web (https://access.clarivate.com/login?app=endnote) so that duplicate studies were excluded. Two independent reviewers (FSC and DCS) assessed the titles based on the eligibility criteria. If selected, the article was submitted to full-text reading (Kappa = 0.86). In case of disagreement among the two reviewers, a third reviewer (HMH) decided whether or not the study should be included. The complete reading of selected studies was then performed by a reviewer (FSC) to verify the eligibility criteria. The complete flowchart of the selection process of the included articles for qualitative and quantitative analysis the process is shown in Figure 1.

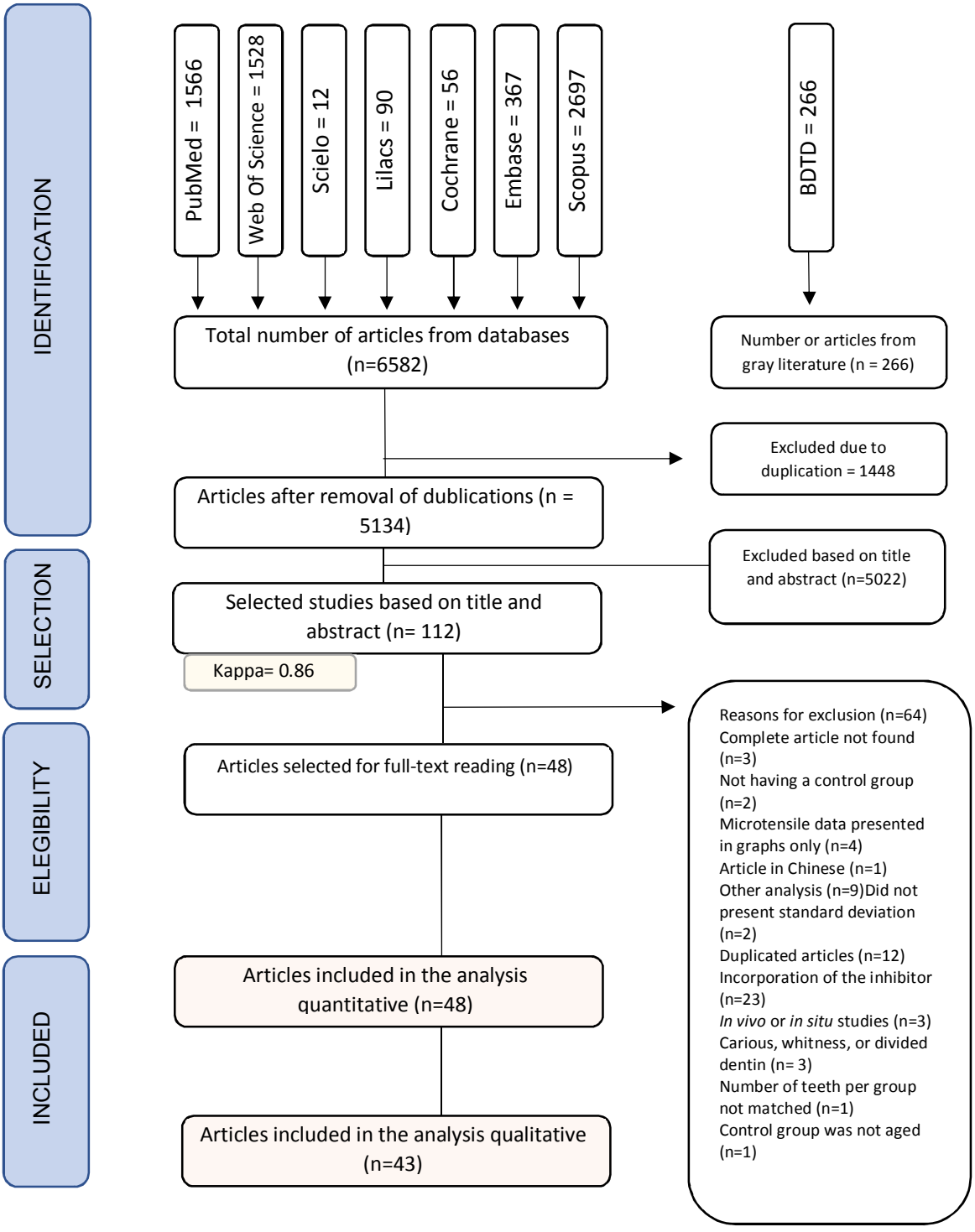


Fig 1. Flowchart of study selection based on the PRISMA strategy.

Data extraction

A standardized protocol for data collection was developed by two authors (HMN and FSC) using a Microsoft Excel spreadsheet. The main data were extracted for the meta-analysis, including surname of first author and year of publication, type of study, type of tooth, aging time, aging process, method of application, MMP inhibitor, and mean and standard deviation of bond strength values in the test and control groups.

Due to the great variability of the adhesive systems used in the selected studies, these were divided according to the mode of application (etch-and-rinse and self-etching), not taking into account whether these systems were simplified or not. Only studies that reported data of inhibitors using both modes of application were included.

Risk of bias assessment

Two independent authors performed the risk of bias assessment (FSC and DCS) based on the Montagner et al. (2014) and Sarkis-Onofre et al. (2014) studies considering the following criteria: randomization of teeth, caries-free teeth or restorations, materials used according to manufacturer's instructions, single operator for the adhesive procedure, sample size calculation, and blinding of the test machine operator. Studies that reported 2 or less criteria were considered as having high risk of bias, 3 or 4 as medium risk of bias, and 5 or 6 as low risk of bias. A quantitative analysis including only studies that presented medium and low risk of bias was performed and results were compared with those of the analysis with high risk of bias studies.

Data analysis

All the available data were used for analysis, allowing one or more data combinations in a single article if aging time varied, such as chlorhexidine 0.2% versus control (initial) and chlorhexidine 0.2% versus control (at 6 months). For the quantitative analysis between control and experimental groups, the gross mean and standard deviation of each article were used. The Comprehensive Meta-Analysis (Biostat, Englewood, NJ, USA) software was used, considering a level of significance of 0.05.

The heterogeneity between studies was assessed by the inconsistency test (I^2) in which values greater than 75% (range 0 to 100) indicate high heterogeneity[42].

Thus, when heterogeneity was less than 75% the fixed-effect model was used and when 75% or greater the random effect model was used. The analyzes performed for each MMP inhibitor and their concentrations are described in Table 1.

Due to the great variability in inhibitor concentrations, only the inhibitory agent was used in the meta-analysis, and not its concentration. Subgroup analyzes were performed for each tested agent, so that their individual influence on the final result could be evaluated.

Table 1

Relation between each inhibitor and its concentrations according to the aging time

Initial	6 months	12 or more months
CHX 0.002% vs. control	CHX 0.002% vs. control	CHX 0.2% vs. control
CHX 0.004% vs. control	CHX 0.02% vs. control	CHX 1% vs. control
CHX 0.02% vs. control	CHX 0.2% vs. control	CHX 2% vs. control
CHX 0.12% vs. control	CHX 1% vs. control	CHX 2.2% vs. control
CHX 0.2% vs. control	CHX 2.2% vs. control	CHX 1.11% vs. control
CHX 1% vs. control	CHX 2% vs. control	EDC vs. control
CHX 2.2% vs. control	EDC vs. control	Riboflavin 0.1% vs. control
CHX 2% vs. control	EGCG 0.02% vs. control	
CHX 4% vs. control	EGCG 0.1% vs. control	
CHX 5% vs. control	EGCG 0.5% vs. control	
CHX 1.11% vs. control	EGCG 2% vs. control	
EDC vs. control		
EGCG 0.1% vs. control		
EGCG 0.02% vs. control		
EGCG 0.5% vs. control		
EGCG 2% vs. control		
GD 5-10% vs. control		
GD 5-8% vs. control		
GD 5% vs. control		
PA 10 vs. control		
PA 15% vs. control		
PA 6.5% vs. control		
Riboflavin 0.1% vs. control		

CHX, chlorhexidine; PA, proanthocyanidin; GD, glutaraldehyde; EDC, carbodiimide; EGCG, epigallocatechin-3-gallate.

RESULTS

Initially, 6582 studies were found and 5134 remained after removal of 1448 duplicates. After assessment of titles and abstracts, 112 were selected for full-text reading. Finally, 43 studies [8,23-25,27-29,43-77] from 2008 to 2018 were included in the meta-analysis (Figure 1) and another 5 articles [32,78-81] were included in the qualitative analysis.

Characteristics of the studies

Most of the selected studies used permanent teeth, except the studies by Soares, et al., 2008 [72] and Lenzi, et al., 2014 [59] that used bovine and deciduous teeth, respectively. Regarding MMP inhibitors, the most used solution was chlorhexidine digluconate at 2 and 0.2% concentrations. The most used aging solutions were deionized water and artificial saliva. The most used adhesive system was Adper Single Bond 2 (3M ESPE), a etch-and-rinse two-step adhesive system. Of the selected studies, 36 were published in English and seven in Portuguese, the latter being theses and dissertations found in the gray literature. The characteristics of the included studies are presented in Table 2.

Table 2

Characteristics of the studies included in the Systematic Review and Meta-Analysis that used metalloproteinase inhibitors, initial or aged for 6, 12 or more months.

Study	Type of aging	Inhibitor of MMP	Adhesive system	Time of aging	Cement
Abu Nawareg et al., 2016	Destilled water	CHX 2%	Adper Single Bond 2 (3 M ESPE)	Initial, 6 and12 months	-
Breschi et al., 2010	Artificial saliva	CHX 0.2%; 2%	Adper Scotchbond 1XT (3 M ESPE)	Initial and 24 months	-
Breschi et al., 2009	Artificial saliva	CHX 0.2%; 2%	Adper Scotchbond 1XT (3 M ESPE), XP Bond (Dentsply)	Initial, 6 and 12 months	-
Costa, 2013	-	CHX 2%; EGCG 0.1%	Clearfil SE Bond (Kuraray)	Initial	-
Cova et al., (2011)	Artificial saliva	RIBOFLAVIN 0.1%	XP Bond (Dentsply)	Initial and 12 months	
Daood et al., 2017	Artificial saliva	quaternary ammonium silane 10%; 2%; 5%; CHX 2%	Adper Single Bond 2 (3 M ESPE), Prime&Bond NT (Dentsply)	Initial, 6 and12 months	-
Delgado, 2015	Artificial saliva	EDC; EDC PRIMER	Adper Scothbond Multi (3M ESPE)	Initial and 6 months	-
Ekambaram et al., 2014	Artificial saliva	CHX 2%	EXPERIMENTAL	Initial and 12 months	-
Erhardt, Osorio, and Toledano, 2008	-	CHX 5%	Adper Scotchbond 1XT (3 M ESPE)	Initial	-

Francisconi-dos-Rios et al., 2015	Artificial saliva	CHX 2%	Adper Single Bond 2 (3 M ESPE)	Initial, 6 and 12 months	-
Gerhardt et al., 2016	Distilled and deionized water	CHX 2%; EGCG 2%	Clearfil SE Bond (Kuraray)	Initial and 6 months	-
Giacomini et al., 2017	Artificial saliva	CHX 2%	Adper Single Bond Universal (3M ESPE)	Initial and 6 months	-
Gunaydin, Yazici, and Cehreli, 2016	-	CHX 2%	Adper Single Bond 2 (3 M ESPE), Clearfil SE Bond (Kuraray), Adper Prompt-L-Pop (3M ESPE)	Initial	-
Hass et al., 2016	Destilled water	GD 5%; PA 6.5%; RIBOFLAVIN 0.1%	Adper Single Bond Plus (3 M ESPE), Tetric N-Bond (Ivoclar)	Initial and 18 months	-
Hiraishi et al., (2009)	-	CHX 2%	Adper Single Bond 2 (3 M ESPE)	Initial	Panavia F2.0 (Kuraray) RelyX Unicem (3M ESPE) RelyX ARC (3M ESPE)
Lee and Sabatini, 2017	Simulated body fluid	GD 5-10%; GD 5-8%	Gluma Comfort Bond (Heraeus Kulzer)	Initial and 6 months	-

Lenzi et al., 2014	Destilled water	CHX 2%	Adper Single Bond (3M ESPE)	Initial and 6 months	-
Lin et al. 2013	Aqueous solution of chloramine at 0.5%	CHX 2%; 0.2%	-	6 months	Panavia F2.0 (Kuraray) RelyX Unicem (3M ESPE)
Liu et al., 2014	Collagenase type II challenge	CHX 2%; PA 10%; 15%	Adper Single Bond 2 (3 M ESPE)	Initial	-
Loguercio et al., 2016/1	Destilled water	CHX 2%	Prime&Bond NT (Dentsply), Adper Single Bond 2 (3 M ESPE)	Initial and 24 months	-
Loguercio et al., 2016/2	Destilled water	CHX 2%	Prime&Bond NT (Dentsply), Adper Single Bond 2 (3 M ESPE)	Initial and 60 months	-
Loguercio et al., 2009	Destilled water	CHX 0.002%; 0.02%; 0.2%; 2%; 4%	Prime & Bond 2.1 (Dentsply), Adper Single Bond (3M ESPE)	Initial and 6 months	-
Luhrs et al., 2013	Destilled water	Galardin, CHX 2%	-	6 months	Clearfil SA (Kurara), RelyX Unicem (3M ESPE), Nexus 3/Optibond (Kerr)
Manso et al., 2014	Destilled water	CHX 1% - water; CHX 1% - ethanol	All Bond 3 (Bisco Inc.), Excite (Ivoclar Vivadent)	Initial, 6 and 15 months	-

Mazzoni et al., 2013	Artificial saliva	EDC	Optibond FL (Kerr), Adper Scotchbond 1XT (3 M ESPE)	Initial and 12 months	-
Mazzoni et al., 2018	Artificial saliva	EDC	Clearfil SE Bond (Kuraray), XP Bond (Dentsply)	Initial and 12 months	-
Montagner, 2013	Destilled water	CHX 2%	Adper Single Bond 2 (3 M ESPE)	Initial and 18 months	-
Perote, 2016	-	CHX 0.2%	Adper Single Bond Universal (3M ESPE)	Inicial	-
Perote et al., 2015	Artificial saliva	CHX 0.02%	Adper Single Bond 2 (3 M ESPE)	Initial and 6 months	-
Sabatini, Kim, and Alias, 2014	Artificial saliva	CHX 2%	Adper Single Bond Plus (3 M ESPE)	Initial and 6 months	-
Sabatini, Ortiz, and Pashley, 2015	Simulated body fluid	CHX 2%	Adper Single Bond Plus (3 M ESPE)	Initial and 24 months	-
Sadek et al., 2010	Artificial saliva	CHX 2%	EXPERIMENTAL, Adper Scothbond Multi (3M ESPE), Adper Single Bond 2 (3 M ESPE)	Initial and 18 months	-

Sanabe, 2009	-	CHX 2%	Adper Single Bond 2 (3 M ESPE), Clearfil SE Bond (Kuraray), Adper Prompt-L-Pop (3M ESPE), Adper Scothbond Multi (3M ESPE)	Initial	-
Santiago et al., 2013	Sodium azide	EGCG 0.02%; 0.1%; 0.5%; CHX 2%	Adper Single Bond 2 (3 M ESPE)	Initial and 6 months	-
Scaffa, 2012	Artificial saliva	CHX 0.2%; 2.2%; 22%	Adper Single Bond 2 (3 M ESPE)	Initial, 6 and 18 months	-
Scheffel et al., 2015	Artificial saliva	EDC	Adper Single Bond Plus (3 M ESPE)	Initial, 6 and 12 months	-
Soares et al., 2008	-	CHX 0.12%; 2%	Adper Single Bond 2 (3 M ESPE)	Initial	-
Souza, 2015	-	CHX 0.2%	Adper Single Bond Plus (3 M ESPE)	Initial	-
Stanislawczuk et al., 2009	Destilled water	CHX 2%	Prime&Bond NT (Dentsply), Adper Single Bond 2 (3 M ESPE)	Initial and 6 months	-
Stape et al., 2012	Artificial saliva	CHX 2%	Adper Scothbond Multi (3M ESPE)	Initial and 48 months	RelyX ARC (3M ESPE) e RelyX U100 (3M ESPE)
Stape et al., 2014	Artificial saliva	CHX 2%	Adper Scothbond Multi (3M ESPE)	Initial	RelyX ARC (3M ESPE) e RelyX U100 (3M ESPE)

Talungchit et al., 2014	Sodium azide	CHX 2%	EXPERIMENTAL	Initial and 24 months	-
Tekce et al., 2016	Destilled water	CHX 2%	Single Bond Universal (3M ESPE) e ALL-BOND UNIVERSAL (Bisco)	Initial and 12 months	-

All selected studies used permanent teeth, except Soares et al., 2008 and Lenzi et al., 2014 who used bovine and deciduous teeth respectively.

MMP, matrix metalloproteinase.

Of the 43 studies included, none had a low risk of bias, 53.4% (23) presented a medium risk, and 46.6% (20), a high risk of bias. These results are described in Table 3.

Table 3

Bias risk of included studies considering the factors described in Materials and Methods.

Study	TR	TFCR	MUAMI	APSP	SZC	BOTM	RISCK
Abu Nawareg et al., 2016	Y	Y	Y	N	N	N	MEDIUM
Breschi et al., 2009	Y	Y	Y	N	N	N	MEDIUM
Breshi et al., 2010	Y	Y	Y	N	N	N	MEDIUM
Costa, 2013	Y	Y	Y	N	N	N	MEDIUM
Cova et al., 2011	Y	Y	Y	N	N	N	MEDIUM

Daood et al., 2017	Y	Y	Y	N	N	N	MEDIUM
Delgado, 2015	Y	Y	Y	N	N	N	MEDIUM
Ekambaram et al., 2014	Y	Y	N	Y	N	N	MEDIUM
Erhardt, Osorio, and Toledano, 2008	N	Y	Y	N	N	N	HIGH
Francisconi-dos-Rios et al., 2015	N	Y	N	N	N	N	HIGH
Gerhardt et al., 2016	Y	N	Y	N	N	N	HIGH
Giacomini et al., 2017	N	Y	Y	N	N	N	HIGH
Gunaydin, Yazici, and Cehreli, 2016	Y	Y	Y	N	N	N	MEDIUM
Hass et al., 2016	Y	Y	N	N	N	N	HIGH
Hiraishi et al., 2009	Y	Y	Y	N	N	N	MEDIUM
Lee and Sabatini, 2017	Y	Y	Y	N	N	N	MEDIUM
Lenzi et al., 2014	Y	Y	N	N	N	N	HIGH
Lin et al., 2013	N	Y	Y	N	N	N	HIGH
Liu et al., 2014	Y	Y	N	N	N	N	HIGH
Loguercio et al., 2016/1	N	Y	Y	N	N	N	HIGH
Loguercio et al., 2016/2	Y	Y	Y	Y	N	N	MEDIUM

Loguercio et al., 2009	N	Y	Y	Y	N	N	MEDIUM
Luhrs et al., 2013	Y	N	Y	N	N	N	HIGH
Manso et al. 2014	Y	Y	N	N	N	N	HIGH
Mazzoni et al., 2013	Y	Y	Y	N	N	N	MEDIUM
Mazzoni et al., 2018	Y	Y	Y	N	N	N	MEDIUM
Montagner, 2013	Y	Y	Y	N	N	Y	MEDIUM
Perote, 2016	N	N	N	N	N	N	HIGH
Perote et al., 2015	Y	Y	Y	N	N	N	MEDIUM
Sabatini, Kim, and Alias, 2014	Y	Y	Y	N	N	N	MEDIUM
Sabatini, Ortiz, and Pashley, 2015	Y	Y	Y	N	N	N	MEDIUM
Sadek et al., 2010	Y	N	Y	N	N	N	HIGH
Sanabe, 2009	Y	Y	Y	N	N	N	MEDIUM
Santiago et al., 2013	N	Y	Y	N	N	N	HIGH
Scaffa, 2012	Y	N	Y	N	N	N	HIGH
Scheffel et al., 2015	Y	Y	Y	N	N	N	MEDIUM
Soares et al., 2008	Y	N	Y	N	N	N	HIGH

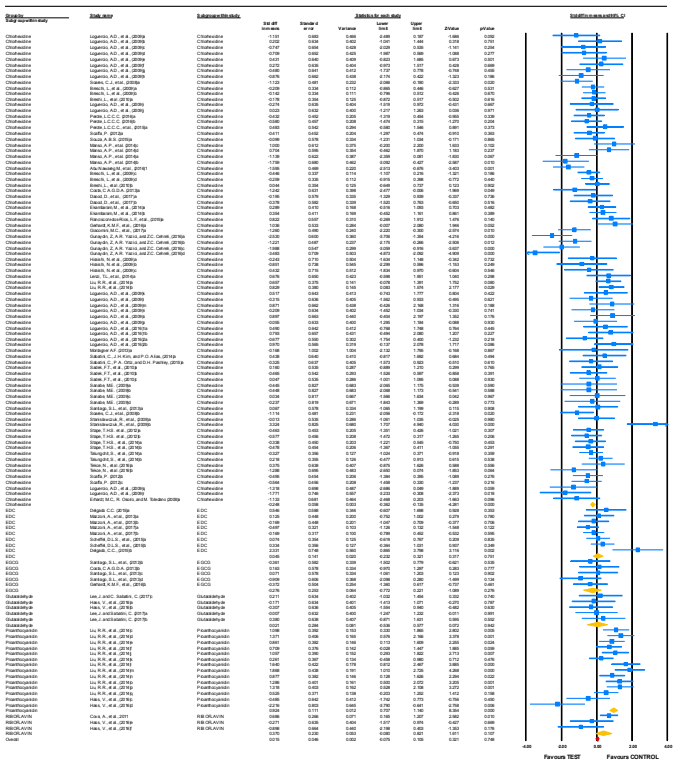
Souza, 2015	Y	Y	Y	N	N	N	MEDIUM
Stanislawczuk et al., 2009	N	Y	N	Y	N	N	HIGH
Stape et al., 2012	Y	Y	N	N	N	N	HIGH
Stape et al., 2014	Y	Y	N	N	N	N	HIGH
Talungchit et al., 2014	Y	Y	N	N	N	N	HIGH
Tekce et al., 2016	N	Y	Y	Y	N	N	MEDIUM

Y (yes); N (no).

* TR, randomization of teeth; TFCR, caries-free teeth or restorations; MUAMI, materials used according to the manufacturer's instructions; APSP, adhesive procedure performed by a single operator; SZC, calculation of sample size; BOTM blinding operator's test machine.

Meta-analysis

The analysis was performed at three time-points: initial (at 24 h), at 6 months, and at 12 months or longer. The first meta-analysis for the initial time-point (inhibitors versus controls) included 117 comparisons from 41 studies that grouped inhibitors of various concentrations (Table 1) evaluating the initial bond strength. Concerning subgroup analysis, the results of bond strength were higher for the test group only when chlorhexidine was used ($p<0.05$). For the group that used proanthocyanidin solutions, bond strength values were lower when compared to the control group; the other tested inhibitors presented bond strength values similar to the control group. However, the overall analysis showed no significant difference between groups, with p = 0.748 (95% confidence interval: 0.075-0.105 and fixed effect model, I^2 = 64.72%) (Figure 2).

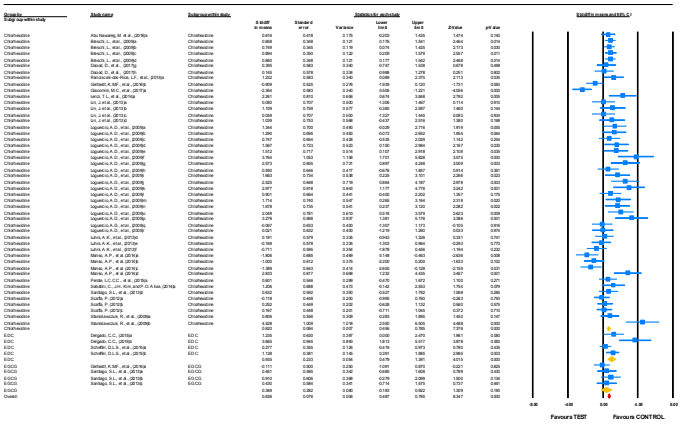


Meta Analysis

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chlorhexidine	82	-0.248	0.058	0.003	-0.362	-0.135	-4.281	0.000	178.013	81	0.000	54.498	0.332	0.100	0.010	0.576
EDC	8	0.045	0.141	0.020	-0.232	0.321	0.317	0.751	14.291	7	0.046	51.019	0.171	0.184	0.034	0.414
EGCG	5	-0.276	0.253	0.064	-0.772	0.221	-1.089	0.276	2.086	4	0.720	0.000	0.000	0.228	0.052	0.000
Glutaraldehyde	5	0.021	0.284	0.081	-0.536	0.577	0.072	0.942	0.766	4	0.943	0.000	0.000	0.285	0.081	0.000
Proanthocyanid	14	0.924	0.111	0.012	0.707	1.140	8.354	0.000	35.706	13	0.001	63.592	0.301	0.189	0.036	0.548
RIBOFLAVIN	3	0.370	0.230	0.053	-0.080	0.821	1.611	0.107	6.084	2	0.048	67.125	0.530	0.815	0.665	0.728
Total within									236.946	111	0.000					
Total between									91.896	5	0.000					
Overall	117	0.015	0.046	0.002	-0.075	0.105	0.321	0.748	328.842	116	0.000	64.725	0.452	0.098	0.010	0.673
Random effects analysis																
Chlorhexidine	82	-0.269	0.086	0.007	-0.436	-0.101	-3.141	0.002								
EDC	8	0.166	0.243	0.059	-0.311	0.643	0.682	0.495								
EGCG	5	-0.278	0.349	0.122	-0.962	0.407	-0.795	0.426								
Glutaraldehyde	5	0.021	0.371	0.138	-0.707	0.748	0.056	0.955								
Proanthocyanid	14	0.865	0.183	0.034	0.505	1.224	4.712	0.000								
RIBOFLAVIN	3	0.052	0.421	0.178	-0.774	0.878	0.124	0.901								
Total between									32.689	5	0.000					
Overall	117	0.106	0.251	0.063	-0.385	0.598	0.424	0.672								

Fig 2. Meta-analysis by subgroups (CHX, EDC, EGCG, GD, PA e RIBOFLAVIN vs. control), using fixed effect model, initial time (up to 24 hours).

The second meta-analysis for the 6-month time-point included 56 comparisons from 18 studies (Table 1). At 6 months, lower values of bond strength were found for groups using CHX and EDC solutions when compared to the control group. The EGCG group presented similar bond strength to the control group (Figure 2). Thus, the overall analysis showed significant differences between the groups ($p<0.05$, 95% confidence interval: 0.487-0.785 and fixed effect model, $I^2 = 68.70\%$), with bond strength significantly higher for the control group (Figure 3).

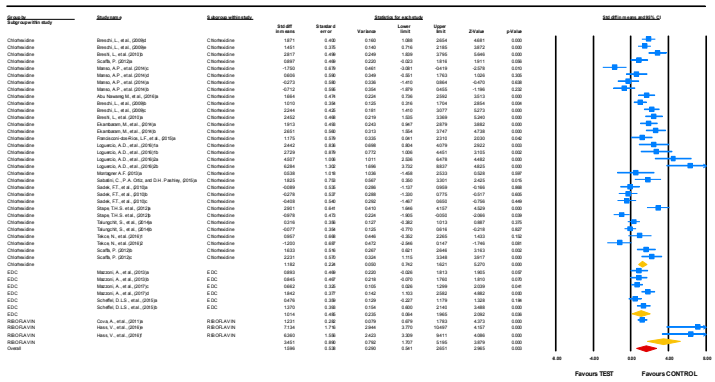


Meta Analysis

Groups	Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chlorhexidine	48	0.620	0.084	0.007	0.456	0.785	7.376	0.000	159.141	47	0.000	70.467	0.018	0.262	0.069	0.304
EDC	4	0.935	0.233	0.054	0.479	1.391	4.015	0.000	12.284	3	0.006	75.579	0.770	0.919	0.845	0.877
EGCG	4	0.369	0.282	0.080	-0.183	0.922	1.309	0.190	1.751	3	0.626	0.000	0.000	0.262	0.069	0.000
Total within									173.176	53	0.000					
Total between									2.575	2	0.276					
Overall	56	0.636	0.076	0.006	0.487	0.785	8.347	0.000	175.751	55	0.000	68.706	0.719	0.217	0.047	0.848
Random effects analysis																
Chlorhexidine	48	0.757	0.156	0.024	0.451	1.064	4.843	0.000								
EDC	4	1.311	0.519	0.270	0.293	2.328	2.525	0.012								
EGCG	4	0.408	0.520	0.270	-0.611	1.427	0.785	0.433								
Total between									1.575	2	0.455					
Overall	56	0.789	0.218	0.048	0.361	1.216	3.614	0.000								

Fig 3. Meta-analysis by subgroups (CHX, EDC and EGCG vs. control), using fixed effect model and 6 months of aging.

The meta-analysis for the 12-month+ time-point included 41 comparisons from 20 studies. Inhibitors were used in various concentrations as shown in Table 1. Subgroup analysis showed that all groups with inhibitors had lower bond strength values than the control group (Figure 4). Therefore, the overall analysis showed a significant difference between the groups ($p <0.05$), in which the control group presented higher bond strength results than the test group (95% confidence interval: 0.541-2.651 and random effect model, $I^2 = 82.162\%$).

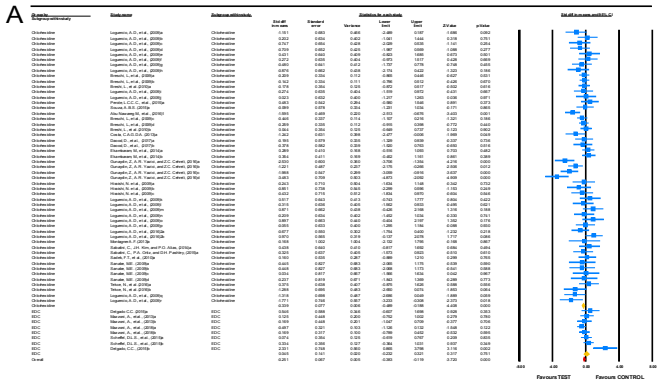


Meta Analysis

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chlorhexidine	32	1.068	0.092	0.009	0.886	1.249	11.546	0.000	190.455	31	0.000	83.723	1.420	0.473	0.224	1.192
EDC	6	0.996	0.158	0.025	0.686	1.306	6.291	0.000	9.249	5	0.100	45.939	0.130	0.179	0.032	0.360
RIBOFLAVIN	3	1.540	0.274	0.075	1.004	2.076	5.629	0.000	21.418	2	0.000	90.662	13.475	16.238	263.661	3.671
Total within									221.122	38	0.000					
Total between									3.114	2	0.211					
Overall	41	1.088	0.077	0.006	0.938	1.238	14.195	0.000	224.237	40	0.000	82.162	1.121	0.344	0.118	1.059
Random effects analysis																
Chlorhexidine	32	1.182	0.224	0.050	0.742	1.621	5.270	0.000								
EDC	6	1.014	0.485	0.235	0.064	1.965	2.092	0.036								
RIBOFLAVIN	3	3.451	0.890	0.792	1.707	5.195	3.879	0.000								
Total between									6.442	2	0.040					
Overall	41	1.596	0.538	0.290	0.541	2.651	2.965	0.003								

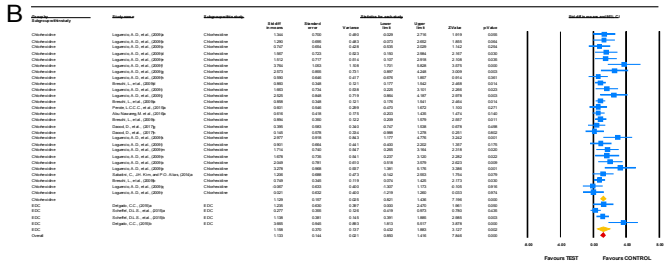
Fig 4. Meta-analysis by subgroups (CHX, EDC and RIBOFLAVIN vs. control), using random effect model and 12 months of aging.

Another meta-analysis (Figure 5) was done to verify the effect of excluding studies with a high risk of bias. For the baseline analysis, 59 comparisons from 22 studies were included. Bond strength was higher for the test group compared to the control group only when chlorhexidine was used. For the EDC group, the bond strength values were similar to the control. The general analysis showed a significant difference between groups with $p < 0.05$ (confidence interval -0.083-0.197, fixed-effect model and I2 = 50.45%), with values of bond strength significantly higher for the test group. At 6 months, 31 comparisons from 8 studies were included and showed lower bond strength values for the chlorhexidine and EDC groups compared to the control group, with $p < 0.05$ (confidence interval 0.802-1.190, fixed-effect model and I2 = 43.90%). At 12 months or more, 21 comparisons from 11 studies were included, from which similar results to the 6-month analysis were found, with significantly lower bond strength values for chlorhexidine and EDC solutions (confidence interval 0.635-2.325, random effect model and I^2 = 75.27%). The results found in the above meta-analyzes are similar to those in which all studies were included.



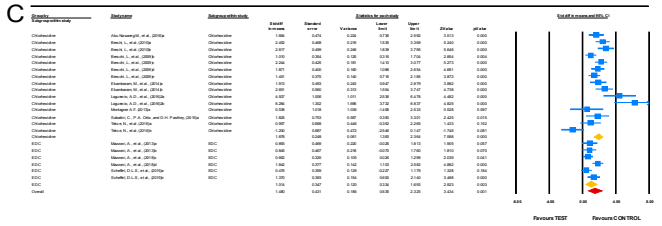
Meta Analysis

Groups	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chlorhexidine	51	-0.339	0.077	0.006	-0.489	-0.188	-4.408	0.000	97.085	50	0.000	48.499	0.286	0.123	0.015	0.535
EDC	8	0.045	0.141	0.020	-0.232	0.321	0.317	0.751	14.291	7	0.046	51.018	0.171	0.184	0.034	0.414
Overall	59	-0.251	0.067	0.005	-0.383	-0.119	-3.720	0.000	117.069	58	0.000	50.457	0.276	0.107	0.011	0.525
Random effects analysis																
Chlorhexidine	51	-0.375	0.109	0.012	-0.589	-0.161	-3.429	0.001								
EDC	8	0.161	0.237	0.056	-0.304	0.625	0.678	0.498								
Overall	59	-0.140	0.264	0.070	-0.667	0.370	-0.561	0.575								



Meta Analysis

Groups	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chlorhexidine	27	1.009	0.110	0.012	0.795	1.224	9.211	0.000	41.114	26	0.030	36.761	0.193	0.151	0.023	0.439
EDC	4	0.935	0.233	0.054	0.479	1.391	4.015	0.000	12.264	3	0.006	75.539	0.770	0.919	0.845	0.877
Overall	31	0.996	0.099	0.010	0.802	1.190	10.044	0.000	53.462	30	0.005	43.906	0.243	0.150	0.023	0.493
Random effects analysis																
Chlorhexidine	27	1.129	0.157	0.025	0.821	1.436	7.196	0.000								
EDC	4	1.158	0.370	0.137	0.432	1.883	3.127	0.002								
Overall	31	1.133	0.144	0.021	0.850	1.416	7.846	0.000								



Meta Analysis

Groups	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chlorhexidine	15	1.794	0.134	0.018	1.531	2.056	13.412	0.000	56.813	14	0.000	75.358	0.842	0.462	0.214	0.918
EDC	6	0.996	0.158	0.025	0.686	1.306	6.291	0.000	9.249	5	0.100	45.939	0.130	0.179	0.032	0.360
Overall	21	1.461	0.102	0.010	1.261	1.662	14.305	0.000	80.675	20	0.000	75.210	0.677	0.307	0.094	0.823
Random effects analysis																
Chlorhexidine	15	1.878	0.248	0.061	1.393	2.364	7.588	0.000								
EDC	6	1.014	0.347	0.120	0.334	1.693	2.923	0.003								
Overall	21	1.480	0.431	0.186	0.635	2.325	3.434	0.001								

Fig 5. Forest plots from studies with medium risk of bias. Initial vs. control (A); 6 months vs. control (B); 12 months or more vs. control (C).

A meta-analysis (Figure 6) was also performed to compare the application modes of the adhesive systems (etch-and-rinse and self-etching) used in the selected studies. Inhibitors that had enough data to allow comparison (minimum of 2 different studies) for this analysis were CHX and EGCG at baseline.

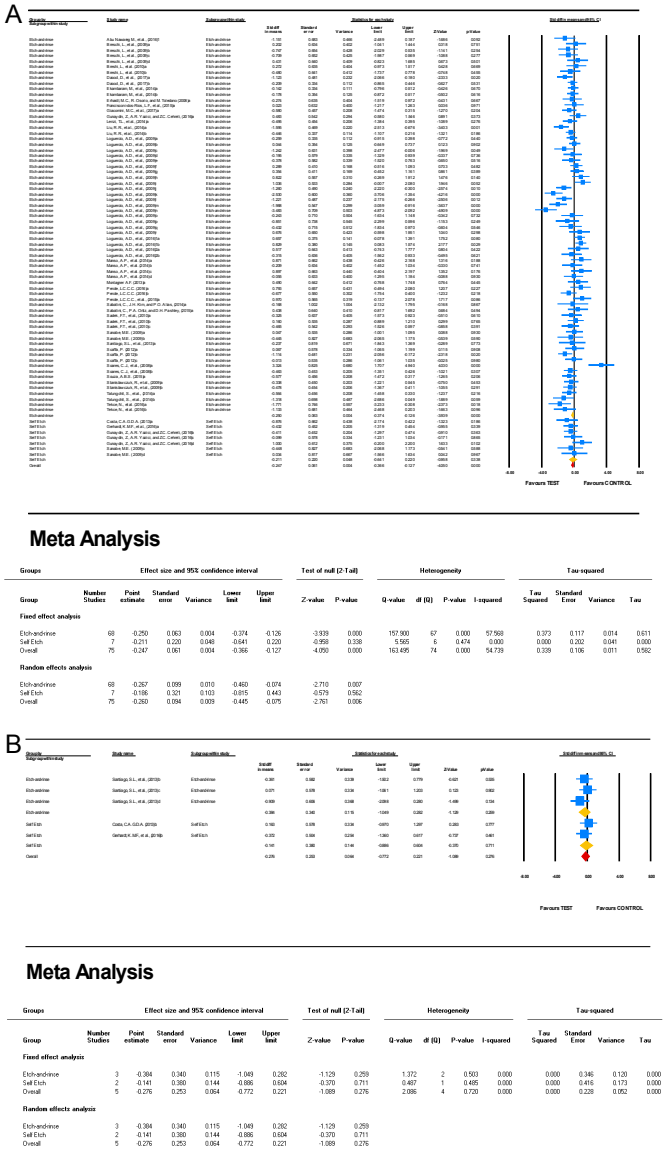


Fig 6. Forest plots of application mode of adhesive systems (etch-and-rinse and self-etching). CHX (A); EGCG (B).

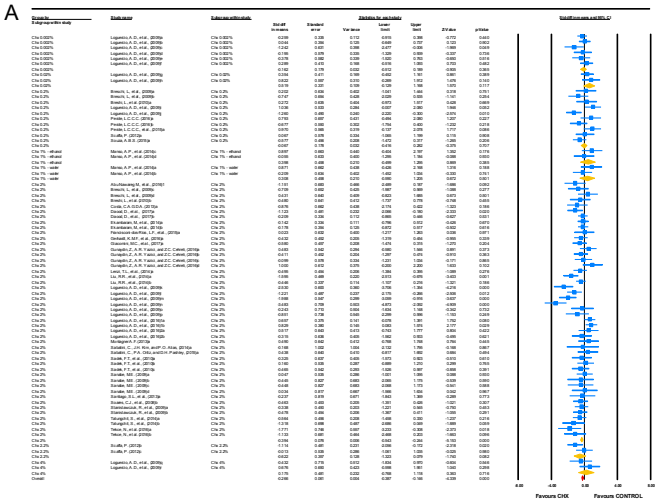
For CHX at the initial time-point (inhibitor versus control), the etch-and-rinse adhesive systems presented higher bond strength values when compared to the control (p = 0.00). For the self-etching mode, there was no significant difference when compared to the control group (p = 0.338). The general analysis showed a difference between groups with p = 0.00 (confidence interval -0.366-0.127, fixed-effect model and I^2 heterogeneity = 54.73%), in which the test group (CHX) had higher values when compared to the control group. For EGCG analysis, EGCG showed no significant difference for both modes of application when compared to the control (etch-and-rinse p = 0.259, self-conditioning p = 0.711). As for the general analysis, there was no difference between the application modes (p = 0.720 confidence interval -0.772, -0.221, fixed-effect model and I^2 = 0%).

Since chlorhexidine was the only inhibitor to present higher bond strength values when compared to control, a more detailed analysis was performed (Figure 7) to verify which concentrations would demonstrate significant values compared to the control group. In the initial time-point, only the 2% concentration showed higher bond strength values than the control group. The general analysis showed a significant difference between groups with p <0.05 (95% confidence interval: 0.387, -0.146 and fixed effect model, I^2 = 50.22%), with bond strength significantly higher for the test group.

At 6 months, the 0.002, 0.2, and 2% concentrations resulted in lower bond strength values than the control group; the other groups had similar results among them. The general analysis showed significant differences between the groups, p <0.05 (95% confidence interval: 0.509-0.860 and fixed effect model, I^2 = 73.20%), with bond strength significantly higher for the group control.

At 12 months or more, 0.2, 2.2, and 2% concentrations showed lower bond strength values than the control group. The other groups showed no difference compared to the control group. The general analysis showed no significant difference between the groups studied, with p=0.063 (95% confidence interval: 0.049-1.906 and random effect model, I^2 = 82.25%).

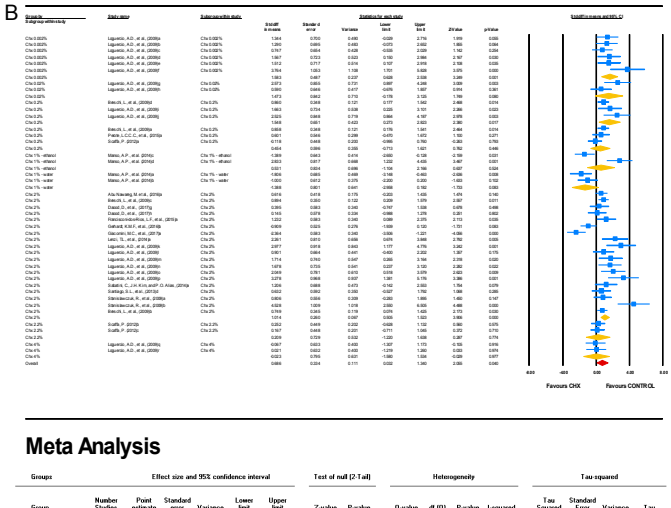
A



Meta Analysis

Groups	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chx 0.002%	6	-0.162	0.179	0.032	-0.512	0.189	-0.905	0.365	4.700	5	0.454	0.000	0.000	0.127	0.016	0.000
Chx 0.02%	2	0.519	0.331	0.109	-0.129	1.168	1.570	0.117	0.456	1	0.500	0.000	0.000	0.339	0.115	0.000
Chx 0.2%	10	-0.067	0.178	0.032	-0.416	0.282	-0.375	0.707	19.093	9	0.022	53.891	0.368	0.327	0.107	0.607
Chx 1%	2	0.398	0.458	0.210	-0.499	1.295	0.869	0.385	1.079	1	0.299	7.338	0.033	0.641	0.411	0.182
Chx 1% - water	2	0.398	0.458	0.210	-0.500	1.295	0.672	0.501	1.389	1	0.238	28.031	0.164	0.825	0.681	0.404
Chx 2%	47	-0.394	0.076	0.006	-0.543	0.244	-5.153	0.000	98.447	46	0.000	53.274	0.315	0.129	0.017	0.561
Chx 2.2%	2	-0.622	0.357	0.128	-1.323	0.079	-1.740	0.082	2.347	1	0.126	57.386	0.348	0.857	0.735	0.590
Chx 4%	2	0.175	0.491	0.232	-0.768	1.118	0.363	0.716	1.315	1	0.252	23.936	0.147	0.869	0.755	0.383
Overall	73	-0.266	0.061	0.004	-0.387	0.145	-4.339	0.000	144.649	72	0.000	50.224	0.279	0.096	0.009	0.528
Random effects analysis																
Chx 0.002%	6	-0.222	0.287	0.082	-0.785	0.340	-0.774	0.439								
Chx 0.02%	2	0.556	0.502	0.252	-0.427	1.539	1.108	0.268								
Chx 0.2%	10	-0.028	0.245	0.060	-0.507	0.452	-0.113	0.910								
Chx 1%	2	0.407	0.589	0.347	-0.747	1.561	0.691	0.489								
Chx 1% - water	2	0.317	0.589	0.347	-0.837	1.471	0.538	0.590								
Chx 2%	47	-0.444	0.112	0.013	-0.663	-0.225	-3.971	0.000								
Chx 2.2%	2	-0.592	0.515	0.265	-1.601	0.417	-1.150	0.250								
Chx 4%	2	0.195	0.607	0.369	-1.035	1.346	0.256	0.798								
Overall	73	-0.094	0.183	0.033	-0.453	0.264	-0.516	0.606								

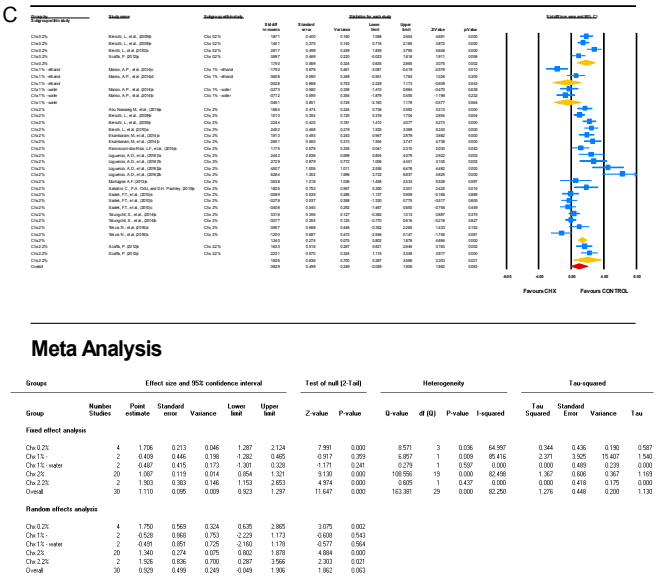
B



Meta Analysis

Groups	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chx 0.002%	6	1.471	0.299	0.089	0.886	2.057	4.926	0.000	6.092	5	0.297	17.922	0.118	0.418	0.175	0.344
Chx 0.02%	2	1.311	0.515	0.266	0.301	2.321	2.543	0.011	3.422	1	0.064	70.781	1.391	2.779	7.723	1.179
Chx 0.2%	3	1.191	0.295	0.087	0.613	1.769	4.038	0.000	3.795	2	0.150	47.294	0.251	0.755	0.570	0.593
Chx 1%	2	0.226	0.505	0.255	-0.764	1.217	0.448	0.654	16.483	1	0.000	93.933	8.373	12.686	159.904	2.894
Chx 1% - water	2	-1.358	0.457	0.208	-2.253	-0.463	-2.974	0.003	0.769	1	0.381	0.000	0.000	0.597	0.356	0.000
Chx 2%	19	0.783	0.131	0.017	0.526	1.039	5.977	0.000	77.689	18	0.000	76.831	1.109	0.537	0.288	1.053
Chx 2.2%	2	0.209	0.317	0.101	-0.412	0.831	0.659	0.510	0.018	1	0.894	0.000	0.000	0.294	0.087	0.000
Chx 4%	2	-0.023	0.447	0.200	-0.900	0.854	-0.051	0.959	0.010	1	0.922	0.000	0.000	0.566	0.320	0.000
Overall	41	0.695	0.089	0.008	0.509	0.860	7.855	0.000	149.273	40	0.000	73.203	0.906	0.307	0.094	0.952
Random effects analysis																
Chx 0.002%	6	1.583	0.487	0.237	0.628	2.538	3.249	0.001								
Chx 0.02%	2	1.473	0.842	0.710	-0.178	3.125	1.749	0.080								
Chx 0.2%	3	1.540	0.651	0.423	0.273	2.823	2.360	0.017								
Chx 1%	2	0.531	0.834	0.696	-1.104	2.166	0.637	0.524								
Chx 1% - water	2	-1.388	0.801	0.641	-2.956	0.182	-1.733	0.083								
Chx 2%	19	1.014	0.260	0.067	0.505	1.523	3.906	0.000								
Chx 2.2%	2	0.209	0.729	0.532	-1.220	1.638	0.287	0.774								
Chx 4%	2	-0.023	0.795	0.631	-1.588	1.534	-0.029	0.977								
Overall	41	0.686	0.334	0.111	0.032	1.340	2.055	0.040								

C



Meta Analysis

Groups	Effect size and 95% confidence interval						Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Chx 0.2%	4	1.706	0.213	0.046	1.287	2.124	7.991	0.000	8.571	3	0.036	64.997	0.344	0.436	0.190	0.587
Chx 1% -	2	0.409	0.446	0.198	-1.282	0.465	-0.917	0.359	6.957	1	0.008	85.416	2.371	3.525	15.407	1.540
Chx 1% - water	2	-0.457	0.415	0.173	-1.301	0.328	-1.173	0.241	0.279	1	0.597	0.000	0.000	0.489	0.239	0.000
Chx 2%	20	1.087	0.119	0.014	0.854	1.321	9.130	0.000	108.556	19	0.000	82.498	1.367	0.606	0.367	1.169
Chx 2.2%	2	1.903	0.383	0.146	1.153	2.653	4.974	0.000	0.935	1	0.437	0.000	0.000	0.418	0.175	0.000
Overall	30	1.110	0.095	0.009	0.923	1.297	11.647	0.000	163.381	29	0.000	82.250	1.276	0.448	0.200	1.130
Random effects analysis																
Chx 0.2%	4	1.750	0.569	0.324	0.635	2.865	3.075	0.002								
Chx 1% -	2	-0.528	0.868	0.753	-2.229	1.173	-0.609	0.543								
Chx 1% - water	2	-0.491	0.951	0.725	-2.160	1.178	-0.577	0.564								
Chx 2%	20	1.340	0.274	0.075	0.802	1.878	4.884	0.000								
Chx 2.2%	2	1.926	0.836	0.700	0.287	3.566	2.303	0.021								
Overall	30	0.929	0.499	0.249	-0.049	1.906	1.862	0.063								

Fig 7. Forest plots CHX concentrations. CHX vs. initial control (A); CHX vs. control 6 months (B); CHX vs. control for 12 months or more (C).

The qualitative analysis included 5 studies [32,78-81] and the results showed that the use of MMP inhibitors does not affect initial bond strength values. However, the studies that performed a long-term evaluation [32,78,79,81] showed that the bond strength values were higher for the inhibitor-treated groups compared to untreated groups.

DISCUSSION

This systematic review showed that the use of MMP inhibitors to maintain the adhesion valours between sound dentin and resin present different results at the initial time-point and after aging. Several inhibitors have been studied to assess their effect on collagen degradation and consequently increase the bond strength of the restorative material to the dental structure; however, only chlorhexidine at the initial analysis presented higher values of bond strength compared to control groups. Thus, the null hypothesis was partially rejected, since in the 6- and 12-month meta-analyses test and control groups did not differ statistically.

This study performed individual and collective comparisons of the influence of MMP inhibitors in bond strength through meta-analyses. Since randomized clinical studies on the bond resistance of restorative materials to the dental structure are not possible, the available evidence is mostly from in vitro studies, which might be a limiting factor of this investigation that should be considered in the interpretation of its results [57].

Although studies on the use of natural solutions [27,28] for inhibiting proteases and strengthening collagen fibrils through more stable bonds have shown promising results [82], this review showed that the use of proanthocyanidin negatively affects the initial bond strength. Perhaps this happens because the effectiveness and stability of the crosslinking treatment depend mainly on the type of PA rich extract and the adhesive system employed, since acetone and ethane can cause dehydration of the dentin matrix, making it even more difficult for the penetration of the adhesive. In addition the concentration and the time of application are important for the performance of this inhibitor. [83, 84]. On the other hand, glutaraldehyde, EGCG, EDC and riboflavin provide similar results to control groups. Moreover, after 6 months of aging, CHX and EDC groups had lower bond strength than controls, and the EGCG group was similar to the control group. After 12 months or more of aging all included inhibitors presented worse results than the control group. These findings are in contrast to several other studies [22-24,40,50,62,82] that show stable bond strength values in the long-term when compared to groups not treated with inhibitors.

For years the most studied MMP inhibitors were CHX, EDC, EGCG and GD with great expectation of success in promoting more stable adhesive interfaces. Currently, several data can be found and the synthesis of these results does not show such promising results after aging. This can be explained by the mechanism of action of these inhibitors, since CHX acts by a mechanism of cation chelation, sequestering metal ions such as zinc and calcium thus inhibiting the catalytic activity of MMPs [85]. Already EDC promotes biomodification of collagen, this is due to the formation of intra and inter molecular ionic covalent bonds, but these ionic bonds do not demonstrate stability after aging [86]. The inhibitory effect of EGCG has also been attributed to zinc chelation, since polyphenols have high affinity for metal ions [29,55]. Like most inhibitors, GD acts by chemical interaction with collagen to increase its resistance, presenting as a disadvantage the difficulty of penetration into the tissue [87,88]. The main action of the MMP inhibitors occurs by chemical interaction and this does not act permanently being this mechanism reversed.

Due to the great variation in inhibitor concentrations, the first analysis did not take into account this parameter. Afterwards, an analysis to evaluate the effectiveness of each concentration of CHX was performed, as CHX presented significant results (Figure 7). The non-specific inhibitory effect of CHX solutions on MMPs has been extensively studied and its action proven [6,7,23,24,34,35]. Some studies have demonstrated the inhibitory effect of CHX at low concentrations, especially after specimen aging [40,62,89], which was not confirmed in this systematic review, in which only the 2% concentration showed higher bond strength values at the initial time-point compared to the control group. This might be explained by the leaching of CHX through the interfaces, thus decreasing its inhibitory potential [2,7].

MMPs are a Ca+ and Zn+ dependent enzyme family capable of degrading various components of the extracellular organic matrix. These enzymes, synthesized and secreted by odontoblasts [90] and activated during adhesive procedures [17], deteriorate the exposed collagen fibrils at the base of the hybrid layer by both etch-and-rinse or self-etching adhesives [17,91]. To decrease degradation, MMP inhibitors are used and a meta-analysis (Figure 6) was developed to compare the effectiveness of these inhibitors. However, in this study, only CHX, at initial evaluation, was effective when used with the etch-and-rinse mode, with no difference to the control group when self-etching adhesives were used. The reason for this result might be that the self-etching systems produce a more regular hybrid layer with smaller area of exposed collagen fibrils when compared to etch-and-rinse systems [92,93]. In addition, many self-etching systems have a chemical interaction with the dental substrate by the action of functional monomers. These monomers may interfere with the action of CHX because, due to the high pH, they form precipitates and because monomers and CHX, which can bind to organic and inorganic components of the substrate, can both bind to calcium [56,94].

The results of the group treated with EGCG (Figure 6-B) showed no difference in the mode of application when compared to the control group. This might have happened because of the various concentrations used, since this parameter was not considered in this analysis. As EGCG is a natural inhibitor that has not yet been thoroughly assessed, further studies should be carried out at various concentrations. Moreover, in this analysis, the results were grouped by the mode of application (etch-and-rinse and self-etching), and not by the number of steps, which is a limitation of this analysis but may help plan future studies on adhesive systems and their effectiveness.

Because a large number of studies presented a high risk of bias, an analysis including only studies with a medium risk of bias was performed (Figure 5). The results did not differ from the results with the overall analyzes (Figures 2, 3 and 4), indicating that studies with a high risk of bias did not negatively interfere with the results.

To avoid a large methodological variability that could compromise the analysis of the data, this systematic review included only studies that evaluated bond strength through microtensile tests. However, some of the analyses presented high heterogeneity, probably due to the studies being carried out by different teams and centers, with different aging protocols, test machines, adhesive systems, and composite resins [40]. In this review, only in vitro studies were considered. However, despite the association between laboratory and clinical data, other factors, such as marginal adaptation and loss of retention [95,96], should also be analyzed to evaluate the effectiveness of an adhesive system, for which further systematic reviews are needed.

The qualitative analysis showed no difference in the initial bond strength between tests and controls, but after aging, the groups treated with MMP inhibitors showed higher values of bond strength. These findings are in contrast to the results of the quantitative analysis. This may have occurred because the inhibitors used are still poorly studied, in addition to the different aging media and adhesive systems used. However, despite the importance of the qualitative data, the greater number of papers included in the quantitative analysis guarantees the production of stronger scientific evidence.

To test the effectiveness of using MMP inhibitors to increase the maintenance of adhesive restorations, four randomized clinical studies with follow-up of up to 36 months [97-100] have shown no difference between test and control groups using the FDI and USPHS criteria. These clinical findings are in line with those found in the present meta-analysis. It is worth emphasizing the importance of the analysis of the laboratory data of these meta-analyzes together with data from clinical studies so that an evidence of greater reliability is generated.

The inhibition of collagen degradation and consequent production of more stable and long-lasting hybrid layers by applying MMP inhibitors was a landmark in Restorative Dentistry. Early in vitro and in vivo studies showed that the use of CHX prior to the application of adhesive systems promoted more stable adhesive restorations in the long term [6,7,21,22,23,101]. Based on such studies, several dental schools adopted clinical protocols that included the use of MMP inhibitors as part of the adhesive step in resin restorations. Later studies with stronger scientific evidence, however, showed that although the initial inhibitory effects were promising, in the long term, the application of these inhibitors was not relevant to the longevity of restoration [38,89-92]. Thus, the use of MMP inhibitors in clinical practice was gradually abandoned, and the results of this systematic review corroborate this trend, since it did not generate strong scientific evidence of the beneficial effect to long-term adhesive stability.

CONCLUSION

Among the various inhibitors studied CHX 2% presented higher bond strength values than the control group in an initial analysis (up to 24 hours), but not after aging. On the other hand, the PA negatively affected the initial values. None of the inhibitors resulted in increased bond strength in the long term. Etch-and-rinse adhesive systems had better results than self-etching systems when using CHX.

The results of previous clinical studies combined to this systematic review with meta-analysis of in vitro studies indicate that there is no evidence to support the use of metalloproteinase inhibitors to increase bond strength between resin and dentin.

Conflict of interest

The authors declare no conflict of interest.

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3 DISCUSSION

3 DISCUSSION

This systematic review with meta-analysis made it possible to compare the influence of inhibitors of metalloproteinase with the control group on bond strength for microtensile tests from *in vitro* studies, either in the early or the aged stages. The results showed that CHX presented superior bond strength results when compared to the other inhibitors at the initial time. However, this result was not repeated in the other studied times and any of the inhibitors proved to be effective after aging when compared to groups without application of these inhibitors. Thus, the null hypothesis was partially rejected, since in the 6- and 12-month meta-analyses test and control groups did not differ statistically.

This study performed individual and collective comparisons of the influence of MMP inhibitors in bond strength through meta-analyses. Since randomized clinical studies on the bond resistance of restorative materials to the dental structure are not possible, the available evidence is mostly from *in vitro* studies, which might be a limiting factor of this investigation that should be considered in the interpretation of its results; bond strength tends to be higher *in vitro* than clinically[29,30].

For the initial results (up to 24 hours) CHX was the only inhibitor that showed favorable results with higher bond strength than the control group (without inhibitors). Although studies on the use of natural solutions[26,31] for inhibiting proteases and strengthening collagen fibrils through more stable bonds have shown promising results[32], this review showed that the use of proanthocyanidin negatively affects the initial bond strength. On the other hand, glutaraldehyde, EGCG, EDC and riboflavin provide similar results to control groups. Moreover, after 6 months of aging, CHX and EDC groups had lower bond strength than controls, and the EGCG group was similar to the control group. After 12 months or more of aging all included inhibitors presented worse results than the control group. These findings are in contrast to several other studies[8,17,27,30-33] that show stable bond strength values in the long-term when compared to groups not treated with inhibitors.

Due to the great variation in inhibitor concentrations, the first analysis did not take into account this parameter. Afterwards, an analysis to evaluate the effectiveness

of each concentration of CHX was performed, as CHX presented significant results. The non-specific inhibitory effect of CHX solutions on MMPs has been extensively studied and its action proven[8,14,18,23,30,36]. Some studies have demonstrated the inhibitory effect of CHX at low concentrations[19,29,35,36], which was not confirmed in this systematic review, in which only the 2% concentration showed higher bond strength values at the initial time-point compared to the control group. This might be explained by the leaching of CHX through the interfaces, thus decreasing its inhibitory potential[18,23].

MMPs are a Ca^{+} and Zn^{+}-dependent enzyme family capable of degrading various components of the extracellular organic matrix. These enzymes, synthesized and secreted by odontoblasts[37] and activated during adhesive procedures[38], deteriorate the exposed collagen fibrils at the base of the hybrid layer by both etch-and-rinse or self-etching adhesives[38-40]. To decrease degradation, MMP inhibitors are used and a meta-analysis was developed to compare the effectiveness of these inhibitors. However, in this study, only CHX, at initial evaluation, was effective when used with the etch-and-rinse mode, with no difference to the control group when self-etching adhesives were used. The reason for this result might be that the self-etching systems produce a more regular hybrid layer with smaller area of exposed collagen fibrils when compared to etch-and-rinse systems[41,42]. In addition, many self-etching systems have a chemical interaction with the dental substrate by the action of functional monomers. These monomers may interfere with the action of CHX because, due to the high pH, they form precipitates and because monomers and CHX, which can bind to organic and inorganic components of the substrate, can both bind to calcium[43,44].

The results of the group treated with EGCG showed no difference in the mode of application when compared to the control group. This might have happened because of the various concentrations used, since this parameter was not considered in this analysis. As EGCG is a natural inhibitor that has not yet been thoroughly assessed, further studies should be carried out at various concentrations. Moreover, in this analysis, the results were grouped by the mode of application (etch-and-rinse and self-etching), and not by the number of steps, which is a limitation of this analysis but may help plan future studies on adhesive systems and their effectiveness.

To verify the influence of studies with high risk of bias in the final results of a meta-analysis, a new analysis excluding high-risk studies was developed. With this, it was observed that the results did not differ from the initial analysis, and it can be concluded that studies with high risk of bias did not negatively interfere in the results of this review. This factor should be taken into account since systematic reviews should be comprehensive enough to avoid bias.

To avoid a large methodological variability that could compromise the analysis of the data, this systematic review included only studies that evaluated bond strength through microtensile tests. However, some of the analyses presented high heterogeneity, probably due to the studies being carried out by different teams and centers, with different aging protocols, test machines, adhesive systems, and composite resins[32]. In this review only *in vitro* studies of bond strength were considered, but several factors influence this type of test, such as type of substrate used, adhesive system, type of surface preparation, tooth type, aging protocol and several other factors[45].

An association between in vitro studies and randomized clinical trials provides a better understanding of these inhibitors. As well as clinical studies with follow-up of up to 36 months[46-49], this review showed no difference in the use of these inhibitors to promote more stable adhesive interfaces after aging.

4 FINAL CONSIDERATIONS

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The use of CHX improves the initial bond strength, but this result was not found in the other evaluated period. None MMP inhibitor solution influenced bond strength values after 6-months aging in *in vitro* studies. In relation to the adhesive systems only etch-and-rinse systems have benefited from the use of CHX.

In conclusion, the use of MMP inhibitors did not promote more stable adhesive bonds after aging as compared to groups without the use of these solutions.

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REFERENCES

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APPENDIXES

APPENDIXES

APÊNCIDE A - DECLARAÇÃO DE USO EXCLUSIVO DE ARTIGO EM DISSERTAÇÃO/TESE

DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN DISSERTATION/THESIS

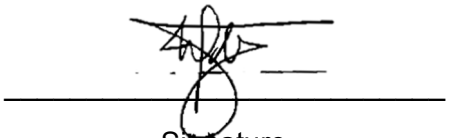
We hereby declare that we are aware of the article (Influence of MMP inhibitors on bond strength of adhesive restorations: systematic review and meta-analysis) will be included in (Dissertation/Thesis) of the student (Francielly da Silva Camim) and may not be used in other works of Graduate Programs at the Bauru School of Dentistry, University of São Paulo.

Bauru, june 3rd, 2019.

Francielly da Silva Camim — Author

Signature

Heitor Marques Honório — Author



Signature

Details on Search Methods to Identify Studies (searched on 28/01/2018)

Strategy
MEDLINE *via* **PubMed**
(((dentin*[tw] OR adhesi*[tw] OR ("dentin-bonding agents"[MeSH Terms] OR "dental bonding"[MeSH Terms] OR bond*[tw]))) AND ((((matrix[tw] OR inhibit*[tw]))) AND (metalloproteinase* OR "metallo proteinase" OR "metallo proteinases" OR metaloproteinase* OR metalloprotease* OR "metallo protease" OR "metallo proteases" OR metaloprotease* OR mmp[tw] OR mmps[tw] OR protease*[tw] OR proteinase*[tw]))) AND ((stability[tw] OR durability[tw] OR long term[tw] OR storage*[tw] OR time factor*[tw] OR aging[tw] OR longevity[tw]))
Web Of Science
Topic: (((dentin* OR adhesi* OR “dentin bonding agent” OR “dentin bonding agents” OR “dental bonding” OR bond*) AND (matrix OR inhibit*) AND (metalloproteinase* OR "metallo proteinase" OR "metallo proteinases" OR metaloproteinase* OR metalloprotease* OR "metallo protease" OR "metallo proteases" OR metaloprotease* OR mmp OR mmps OR protease* OR proteinase*) AND (stability OR durability OR “long term” OR storage* OR “time factor” OR “time factors” OR aging OR longevity))) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI
Scielo
(dentin* OR (adhesi* OR adesi*) OR (“dentin bonding agent”) OR (“dentin bonding agents”) OR (“adesivo dentinario”) OR (“adesivos dentinarios”) OR (“recubrimiento dentinario”) OR (“recubrimientos dentinarios”) OR “dental bonding” OR (“colagem dentaria”) OR (“recubrimiento dental adhesivo”) OR bond* OR adesao) AND (matrix OR matriz OR inhibit* OR inibidor* OR inhibidor*) AND ("metallo protease" OR "metallo proteases" OR "metallo proteinase" OR "metallo proteinases" OR “metalo proteasa” OR “metalo proteasas” OR “metalo protease” OR “metalo proteases” OR “metalo proteinasa” OR “metalo proteinasas” OR “metalo proteinase” OR “metalo proteinases” OR metalloprotease* OR metalloproteinase* OR metalloproteinase* OR metaloproteasa* metaloprotease* OR metaloproteinasa* OR metaloproteinase* OR mmp OR mmps OR protease* OR proteasa* OR proteinase* OR proteinasa*) AND (stability OR estabilidad* OR durability OR durabilidad* OR “long term” OR “longo prazo” OR “largo plazo” OR storage* OR armazena* OR almacena* OR (time factor*) OR (fator tempo) OR (fatores tempo) OR (factor tiempo) OR (factores tiempo) OR aging OR envelhec* OR envejec* OR longevity OR longevidad*)

Lilacs

(tw:(dentin$ OR adhesi$ OR adesi$ OR "dentin bonding agent" OR “dentin bonding agents”)) OR (mh:(“dentin-bonding agents”)) OR (mh:("dental bonding")) OR (tw:(“adesivo dentinário” OR “adesivos dentinarios” OR “recubrimiento dentinario” OR “recubrimientos dentinarios” OR “dental bonding” OR “colagem dentaria” OR “recubrimiento dental adhesivo”)) OR tw:(bond$ OR adesao) AND (tw:(matrix OR matriz OR inhibit$ OR inibidor$ OR inhibidor$)) AND tw:(("metallo protease" OR "metallo proteases" OR "metallo proteinase" OR "metallo proteinases" OR “metalo proteasa” OR “metalo proteasas” OR “metalo protease” OR “metalo proteases” OR “metalo proteinasa” OR “metalo proteinasas” OR “metalo proteinase” OR “metalo proteinases” OR metalloprotease$ OR metalloproteinase$ OR metalloproteinase$ OR metaloproteasa$ metaloprotease$ OR metaloproteinasa$ OR metaloproteinase$ OR mmp OR mmps OR protease$ OR proteasa$ OR proteinase$ OR proteinasa$)) AND (tw:(stability OR estabilidad$ OR durability OR durabilidad$ OR “long term” OR “longo prazo” OR “largo plazo” OR storage$ OR armazena$ OR almacena$ OR (time factor$) OR (fator tempo) OR (fatores tempo) OR (factor tiempo) OR (factores tiempo))) OR (tw:(aging OR envelhec$ OR envejec$ OR longevity OR longevidad$))

Cochrane

#1 (dentin*):ti,ab,kw

#2 (adhesi*):ti,ab,kw

#3 MeSH descriptor: [Dentin-Bonding Agents] explode all trees

#4 MeSH descriptor: [Dental Bonding] explode all trees

#5 (bond*):ti,ab,kw

#6 matrix:ti,ab,kw

#7 (inhibit*):ti,ab,kw

#8 metalloproteinase*

#9 metallo proteinase

#10 metallo proteinases

#11 metaloproteinase*

#12 metalloprotease*

#13 metallo protease

#14 metallo proteases

#15 metaloprotease*

#16 mmp:ti,ab,kw

#17	mmps:ti,ab,kw
#18	(protease*):ti,ab,kw
#19	(proteinase*):ti,ab,kw
#20	stability:ti,ab,kw
#21	durability:ti,ab,kw
#22	long term:ti,ab,kw
#23	(storage*):ti,ab,kw
#24	(time factor*):ti,ab,kw
#25	aging:ti,ab,kw
#26	longevity:ti,ab,kw
#27	{or #1-#5}
#28	#6 or #7
#29	{or #8-#19}
#30	{or #20-#26}
#31	{and #27-#30}

Embase

(dentin*:ab,ti,de OR adhesi*:ab,ti,de OR 'dentin bonding agent'/exp OR 'dental bonding'/exp OR bond*:ab,ti,de) AND (matrix:ab,ti,de OR inhibit*:ab,ti,de) AND (metalloproteinase* OR 'metallo proteinase' OR 'metallo proteinases' OR metaloproteinase* OR metalloprotease* OR 'metallo protease' OR 'metallo proteases' OR metaloprotease* OR mmp:ab,ti,de OR mmps:ab,ti,de OR protease*:ab,ti,de OR proteinase*:ab,ti,de) AND (stability:ab,ti,de OR durability:ab,ti,de OR 'long term':ab,ti,de OR storage*:ab,ti,de OR 'time factor*':ab,ti,de OR aging:ab,ti,de OR longevity:ab,ti,de) [embase]/lim NOT [medline]/lim

Scopus

(TITLE-ABS-KEY ((dentin* OR adhesi* OR "dentin bonding agent" OR "dentin bonding agents" OR "dental bonding" OR bond*)) AND TITLE-ABS-KEY ((matrix OR inhibit*)) AND TITLE-ABS-KEY ((metalloproteinase* OR "metallo proteinase" OR "metallo proteinases" OR metaloproteinase* OR metalloprotease* OR "metallo protease" OR "metallo proteases" OR metaloprotease* OR mmp OR mmps OR protease* OR proteinase*)) AND TITLE-ABS-KEY ((stability OR durability OR "long term" OR storage* OR "time factor" OR "time factors" OR aging OR longevity)))