Review Article

MMP Inhibitors and Dentin Bonding: Systematic Review and Meta-Analysis

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Objectives. Resin-dentin bond strength decreases over time. This reduction is related to the loss of hybrid layer integrity. Collagenolytic enzymes, especially matrix metalloproteinases (MMPs), are responsible for the degradation of the collagen matrix of the hybrid layer. Various MMP inhibitors with the ability to prevent enzymatic degradation have been identified. This study aimed to systematically review the literature for studies which evaluated the effect of MMP inhibitors on the immediate and aged dentin bond strengths. Study Selection: Screening and analysis were carried out by two reviewers. Two databases were searched, and from a total of 740 articles, 43 were accepted for full review. 21 articles with 0.2%–2% chlorhexidine (CHX) treatments were included for meta-analysis. A risk of bias assessment was performed on all studies chosen for meta-analysis. A variety of MMP inhibitors have been studied, CHX being the most widely used. Conclusions. A clear trend for a lower loss of dentin bond strength was observed with different MMP inhibitors. In meta-analysis, no significant difference was seen between the CHX and control in the immediate bond strengths. Bond strengths in the CHX group were significantly higher than the control group after aging ($P < 0.001$). The percentage of fractures occurring at the adhesive interface increased after aging. Five out of 21 studies included in the meta-analysis had high and the rest medium risk of bias. More long-term studies with lower risks of bias should be carried out to increase the reliability of results. Clinical Relevance: The use of MMP inhibition with chlorhexidine can be recommended to increase the longevity of resin-dentin bond strength.

1. Introduction

Studies have shown that the bond between the adhesive systems and dentin weakens over time. This decrease in bond strength is related to the degradation of the hybrid layer [1, 2]. The hybrid layer is the area of adhesion formed by the dentin collagen matrix and resin adhesive. After exposure to acid (etch-and-rinse adhesives) or acidic monomers (self-etch adhesives), the demineralized dentin collagen matrix is infiltrated with the applied adhesive resin [3, 4]. The collagen matrix is vulnerable to enzymatic degradation by the endogenous collagenolytic enzymes, matrix metalloproteinases (MMPs) and cysteine cathepsins, and these enzymes play an important role in bond destruction [2]. MMP inhibitors can prevent the function of these enzymes, with chlorhexidine (CHX), galardin, and benzalkonium chloride being the most widely studied [5, 6]. More recently, collagen cross-linker agents have also been shown to inhibit protease enzymes [7].

Systematic review and meta-analysis by Montagner et al. [8] indicated that CHX is effective in maintaining long-term bond strength. This study aimed to provide an updated systematic review and meta-analysis of the literature involving studies which evaluated the effect of MMP inhibitors on the immediate and aged resin-dentin bond strength. The hypothesis was that MMP inhibitors have a significant effect on the longevity of bond strength, which becomes evident after 6 months.
2. Materials and Methods

In this systematic literature review, two separate electronic databases were used (PubMed and Scopus). Suitable search phrases for both databases were constructed using the following search phrases as a guideline: (matrix metalloproteinase OR MMPs inhibitor OR protease inhibitor OR chlorhexidine OR benzalkonium chloride OR bac*) AND (dentin* adhesive* OR adhesive system* OR hybrid layer* OR bond*) AND (age* OR stability* OR durability* OR strength* OR long-term*) and "cross-linker": e.g., with the following search phrases “grape seed extract AND dentin AND bonding” or “proanthocyanidin AND dentin AND bonding.”

The search phrases for each database were altered and optimized so that the resulting articles were as relevant as possible to the targeted articles. The final search phrases used were as follows:

PubMed: (((((((((proanthocyanidin AND dentin AND bonding) OR (grape seed extract AND dentin AND bonding) OR chlorhexidine* [Text Word] OR "benzalkonium chloride*" [Text Word] OR BAC* [Text Word] OR “matrix metalloproteinase inhibitor*” [Text Word] OR “MMP* inhibitor*” [Text Word] OR "protease inhibitor*" [Text Word] OR [Text Word] OR durab* [Text Word] OR strength* [Text Word] OR long-term* [Text Word])))) AND ((dentin* AND adhesive* [Text Word] OR "adhesive system*" [Text Word] OR "hybrid layer*" [Text Word] OR bond* [Text Word]))) OR ((("matrix metalloproteinase*" [Text Word]) AND ((age* [Text Word] OR stability* [Text Word] OR durab* [Text Word] OR strength* [Text Word] OR long-term* [Text Word]))) AND ((dentin* AND adhesive* [Text Word] OR "adhesive system*" [Text Word] OR "hybrid layer*" [Text Word] OR bond* [Text Word]))) OR ((("matrix metalloproteinase inhibitor*" [Text Word] OR “MMP* inhibitor*” [Text Word]) AND bond strength [Text Word]))) OR ((("Matrix Metalloproteinase Inhibitors" [Mesh]) AND ((("Dental Bonding" [Mesh]: noexp]) OR “Light-Curing of Dental Adhesives [Mesh]" OR “Self-Curing of Dental Resins"[Mesh]))).)

Scopus: (TITLE-ABS-KEY ((proanthocyanidin AND dentin AND bonding) OR (grape seed extract AND dentin AND bonding) OR "matrix metalloproteinase*" OR “MMP* inhibitor*” OR "protease inhibitor*" OR chlorhexidine* OR "benzalkonium chloride*" OR bac*) AND TITLES-ABS-KEY (adhes* "hybrid layer" OR bond*) AND TITLE-ABS-KEY (ag* OR stability* OR durab* OR strength* OR long-term*) AND TITTLE-ABS-KEY (dentin*) AND NOT INDEX (medline) AND (LIMIT-TO (SUBJAREA, "DENT").)

Using these search phrases, 531 articles were found on PubMed and 209 articles on Scopus. The search included all articles published before 5.7.2018. After the database search, screening was performed by two individuals on all articles to single out the relevant ones. For the screening, the following predetermined rejection criteria were used: under 6 months aging (follow-up), thermocycling used for aging, no measured data of bond strength, no MMP inhibitors used during bonding, no control group, review articles, or other interests, e.g., root canal sealers and root canal posts. If any one of these factors was present, the article was rejected. The article also had to be written in English.

The screening was performed in three stages (Figure 1). During the first stage, only the title and the abstract of the article were used to determine whether any of the rejection criteria was present. The initial screening resulted in 126 articles from PubMed and 22 articles from Scopus. During the second stage, the complete text of all remaining articles was read and interpreted by the individual screeners (a total of 148). The same rejection criteria were used, and after careful selection, 59 articles from PubMed and seven articles from Scopus were accepted (n = 66). A final screening was performed with both reviewers present. Five of the seven articles found in Scopus were the same as on PubMed. Furthermore, 18 studies were rejected due to the rejection criteria and lack of available data, leaving 43 accepted articles. In addition, studies done on carious teeth were excluded.

Due to the wide heterogeneity between the studies using other MMP inhibitors than CHX, only data involving 0.2%–2% CHX would be used for the meta-analysis. The 21 chosen articles were allocated into six different comparison groups depending on whether the samples had been aged for 6, 12, or 24 months and whether an etch-and-rinse or self-etching system had been used. No articles were found for the 12-month storage time and self-etch, so this group was excluded. The bond strength, sample size (N), and standard deviation data for the respective storage times and controls were retrieved from the articles. The N for each group represented the total number of teeth used in each comparison group. Pooled effect estimates were attained by comparing the means of each bond strength value, expressed as the raw mean difference among the groups. Statistical heterogeneity of the treatment effect was assessed via the Cochran Q test, with P < 0.05 considered significant, and the inconsistency I² test, in which values > 50% were considered to indicate high heterogeneity. Meta-analysis on the chosen comparison groups was carried out using the MedCalc (version 19.2.1: MedCalc Software Ltd., Ostend, Belgium).

2.1. Assessment of Risk of Bias. The risk of bias evaluation, adapted from a previous study [8], evaluated the following parameters for the study’s quality assessment: randomization, use of intact teeth, use of materials according to the instructions, adhesive procedures performed by the same operator, description of sample size calculation, and blinding of testing. The articles reporting 5 to 6 items were classified as low risk of bias, 3 or 4 as medium risk, and only 1 or 2 as high risk.

3. Results

From the initial 740 articles, 43 articles with altogether 240 groups were subjected to a comprehensive examination (Table 2). Altogether, 21 different enzyme inhibitors were tested. The most commonly used MMP inhibitor was CHX.
To compare CHX vs. control after 12 months aging, 17 data sets from 10 articles were available (Figure 3(b)). Bond strengths in the CHX group were significantly higher than in the control group ($P<0.001$). The heterogeneity between the studies was high (Cochran’s $Q P<0.05$, $I^2$ 75.0%).

The last analysis involved CHX vs. control after 24 months aging, including six data sets from three articles (Figure 3(c)). Bond strengths in the CHX group were significantly higher than in the control group ($P<0.001$). The heterogeneity between the studies was extremely low (Cochran’s $Q P = 0.817$, $I^2$ 0%).

3.2. Risk of Bias. Of the 21 articles selected for the meta-analysis, five were classified as having a high risk and 16 as a medium risk of bias. None of the articles had a low risk of bias (Table 2).

4. Discussion

The general trend of all 43 articles with 21 different collagenolytic enzyme inhibitor protocols demonstrated markedly lower loss of bond strength with enzyme inhibition. Studies involving other MMP inhibitors were excluded from the meta-analysis due to a wide range of heterogeneity in the inhibitors used and a small number of studies for each inhibitor except for CHX. All three comparisons between the CHX-treated and controls after aging for at least six months demonstrated significantly higher bond strength with CHX. Thus, the hypothesis was accepted.

The results of the meta-analysis showed that the use of CHX has no significant effect on immediate resin-dentin bond strength. The finding is in line with a previous study [8]. Two studies [14, 23] have shown a significant decrease in the immediate bond strength of the CHX group compared to the control. After reviewing the articles, no clear explanation for this difference could be identified, although several differences in the application of CHX were noted. Giacomini and co-authors speculated that the use of acidic CHX after acid etching may have resulted in increased collagen exposure, possibly reducing the immediate bond strength [14].

After aging for 6, 12, and 24 months, the meta-analysis demonstrated significantly better bond strength with CHX compared to the control groups. Despite the heterogeneity of the studies, 6- and 12-month analyses indicate the advantage of using CHX to preserve the bond strength. In addition, with the studies evaluating the bond strength after 24 months of aging, the homogeneity of the data was striking ($I^2$ 0%). Indeed, longer aging seems to increase the difference between the bond strengths of CHX and control groups.

The immediate fracture percentage at the adhesive interface was practically the same for MMP inhibitor and control groups, although some isolated differences can be identified. It can generally be observed that as the follow-up time increases, the percentage of fractures occurring at the adhesive interface seems to increase, regardless of enzyme inhibition. This may be due to slow degradation of hybrid layer collagen despite the enzyme inhibition, the hydrolytic degradation of the resin component, or—most likely—to
| Article                  | Adhesive/mixed failure modes (%) in groups immediately/after aging | N  | Technique of bonding (E&R/SE) MMP inhibitor + % | Bond strength reduction (%) after aging |
|-------------------------|------------------------------------------------------------------|----|-----------------------------------------------|-----------------------------------------|
|                         |                                                                  |    | E&R                                           | 6 m          | 12 m          | >12 m        |
| Li et al. [9]           |                                                                  | NA | DMSO 1%                                       | 17.4*        |               |              |
|                         |                                                                  | NA | GD 5%                                         | 11.9*        |               |              |
|                         |                                                                  | NA | BAI 2.5 μg/mL                                  | 10.1*        |               |              |
|                         |                                                                  | NA | Control                                       | 36.0         |               |              |
| Malaquias et al. [10]   | Group: immediate/24 m Ambar®                                     | 50 | E&R                                           | 24 m         |               |              |
|                         |                                                                  |    | CHX 0.01%: 79.2/84.3                           | 16.7*        |               |              |
|                         |                                                                  |    | CHX 0.05%: 81.3/88.1                           | 17.0*        |               |              |
|                         |                                                                  |    | CHX 0.1%: 80.5/86.9                            | 10.0*        |               |              |
|                         |                                                                  |    | CHX 0.2%: 72.7/76.8                            | 10.4*        |               |              |
|                         |                                                                  |    | Control: 81/83.4                               | 40.2         |               |              |
|                         |                                                                  |    | CHX 0.01%: 75.7/77.7                           | 33.8*        |               |              |
|                         |                                                                  |    | CHX 0.05%: 81/78.4                             | 32.1*        |               |              |
|                         |                                                                  |    | CHX 0.1%: 69.8/94.8                            | 29.1*        |               |              |
|                         |                                                                  |    | CHX 0.2%: 74/82.1                              | 29.3*        |               |              |
|                         |                                                                  |    | Control: 81.6/77.2                             | 53.3         |               |              |
|                         | Group: immediate/6 m/12 m MMP8-I/90/70/75                         | 60 | MMP8-I                                       | 1.1*         | 1.8*          |
|                         |                                                                  |    | CHX 2%: 100/95/95                              | 0.7          | 5.3*          |
|                         |                                                                  |    | Control: 95/80/90                              | 17.2         | 24.1          |
| Ou et al. [11]          | Group: immediate/6 m μTBS                                         | 48 | E&R                                           | 30.2         |               |              |
|                         |                                                                  |    | MDPB: 68/74                                    | 58.5         |               |              |
|                         |                                                                  |    | BAC: 68/72                                     | 64.3         |               |              |
|                         |                                                                  |    | Control: 72/78                                 |               |               |              |
| El Gezawi et al. [12]   | 4-point loading                                                  | 48 | E&R                                           | 31.6*        |               |              |
|                         |                                                                  |    | MDPB: 68/70                                    |               |               |              |
|                         |                                                                  |    | BAC: 72/86                                     |               |               |              |
|                         |                                                                  |    | Control: 78/84                                 |               |               |              |
| Maravic et al. [13]     | Group: immediate/12 m ACR                                          | 36 | E&R                                           | 14.4*        |               |              |
|                         |                                                                  |    | ACR 0.01%: 65/90                               | 46.1         |               |              |
|                         |                                                                  |    | Control: 67/82                                 |               |               |              |
| Giacomini et al. [14]   | Group: immediate/6 m                                              | 90 | E&R                                           | 41.8*        |               |              |
|                         |                                                                  |    | Normal dentin                                 |               |               |              |
|                         |                                                                  |    | CHX 2%: 100/100                                | 26.6*        |               |              |
|                         |                                                                  |    | Control: 96/92                                 | 22.3         |               |              |
|                         |                                                                  |    | Artificially carious dentin                    |               |               |              |
|                         |                                                                  |    | CHX 2%: 100/100                                | 9.9          |               |              |
|                         |                                                                  |    | E-64: 96/96                                    | 15.1         |               |              |
|                         |                                                                  |    | Control: 100/100                               | 13.4         |               |              |
|                         |                                                                  |    | Eroded dentin                                 |               |               |              |
|                         |                                                                  |    | CHX 2%: 100/100                                | 10.7*        |               |              |
|                         |                                                                  |    | E-64: 100/100                                  | 8.4          |               |              |
|                         |                                                                  |    | Control/96/100                                 | 12.7         |               |              |
| Article           | Adhesive/mixed failure modes (%) in groups immediately/after aging | Bond strength reduction (%) after aging |
|-------------------|-------------------------------------------------------------------|----------------------------------------|
|                   | Technique of bonding (E&R/SE) MMP inhibitor + %                  | 6 m  | 12 m  | >12 m |
| Daood et al. [15] | E&R                                                               |      |       |       |
|                   | Adper™ Single Bond 2                                               |      |       |       |
|                   | CHX 2%: 64/72                                                      | 4*   | 8*    |       |
|                   | QAS 2%: 52/65                                                     | −8.1*| −3.6* |       |
|                   | QAS 5%: 75/64                                                     | 4.2* | −6.0* |       |
|                   | QAS 10%: 72/67                                                    | 10.5 | 23.1  |       |
|                   | Control: 63/66                                                    | 14.5 | 29.5  |       |
|                   | Prime & Bond® NT™                                                  |      |       |       |
|                   | CHX 2%: 80/55                                                     | 3.3  | 8.8*  |       |
|                   | QAS 2%: 59/64                                                     | −2.2 | −4.4* |       |
|                   | QAS 5%: 74/74                                                     | 5.6* | 11.3* |       |
|                   | QAS 10%: 75/79                                                    | 6.9* | 13.8* |       |
|                   | Control: 64/74                                                    | 12.2 | 20.9  |       |
| Venigalla et al. [16] | RF WWB: 73/47                                                  | 2.5* |       |       |
|                   | CD WWB: 73/60                                                     | 5.6* |       |       |
|                   | PAC WWB: 67/47                                                    | 17*  |       |       |
|                   | Control WWB: 87/60                                                | 24   |       |       |
|                   | RF EWB: 53/47                                                     | 0.6* |       |       |
|                   | CD EWB: 67/60                                                    | 4.7* |       |       |
|                   | PAC EWB: 60/53                                                    | 5.6* |       |       |
|                   | Control EWB: 67/47                                                | 10.2 |       |       |
| Carvalho et al. [17] | Green tea: 36/68                                               | −55.2* |       |       |
|                   | CHX 2%: 66/78                                                    | 1.3  |       |       |
|                   | Control: 81/68                                                    | 11.1 |       |       |
| Barcellos et al. [18] | NA                                                                |       | 3.1*  | 46.1  |
|                   | ZnOn 1 wt.%                                                      |       |       |       |
|                   | Zn-Mt. 1 wt.%                                                    |       |       |       |
|                   | Control                                                           |       | 44.4  |       |
| Hass et al. [19]  | E&R Single Bond Plus®                                             | 18 m |       |       |
|                   | PAC 6.5wt%                                                        | 11.9*|       |       |
|                   | UVA-RF 0.1wt%                                                    | 14.8*|       |       |
|                   | GD 5wt%                                                           | 22.9*|       |       |
|                   | Control                                                           | 64.8 |       |       |
|                   | E&R Tetric N-Bond®                                               |       | 5.5*  |       |
|                   | PAC 6.5wt%                                                        |       |       |       |
|                   | UVA-RF 0.1wt%                                                    | 20.3*|       |       |
|                   | GD 5wt%                                                           | 32.2*|       |       |
|                   | Control                                                           | 62.2 |       |       |
| Loguercio et al. [20] | Group: immediate/24 m                                          |       | 24 m  |       |
|                   | Prime & Bond NT®                                                  |       |       |       |
|                   | MC 2%: 97/94                                                      | 10.6*|       |       |
|                   | CHX 2%: 85/94                                                    | 17.9*|       |       |
|                   | Control: 80/78                                                    | 44.2 |       |       |
|                   | Adper™ Single Bond 2                                               |       |       |       |
|                   | MC 2%: 98/96                                                      | 10.9*|       |       |
|                   | CHX 2%: 93/90                                                    | 13.9*|       |       |
|                   | Control: 93/95                                                    | 30.1 |       |       |
| Hass et al. [21]  | E&R                                                               |       |       |       |
|                   | PAC 2%-PA: 84/82                                                  | −2.7*|       |       |
|                   | Control: 97/100                                                   | 47.2 |       |       |

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Table 1: Continued.

| Article                        | Adhesive/mixed failure modes (%) in groups immediately/after aging | $N$ | Technique of bonding (E&R/SE) MMP inhibitor + % Bond strength reduction (%) after aging |
|-------------------------------|--------------------------------------------------------------------|-----|-------------------------------------------------------------------------------------|
| Tekçe et al. [22]            |                                                                   |     |                                                                                     |
| Group: immediate/12 m         |                                                                   |     |                                                                                     |
| SB Universal®                |                                                                   |     |                                                                                     |
| BAC 1%: 58.5/75.5            |                                                                   |     |                                                                                     |
| CHX 2%: 70.4/76              |                                                                   |     |                                                                                     |
| EDTA 0.5 m: 66.1/73.4        |                                                                   |     |                                                                                     |
| SE: 60.6/78.3                |                                                                   |     |                                                                                     |
| E&R: 58.4/79                 | 50                                                                 |     |                                                                                     |
| BAC 1%: 58.5/75.5            |                                                                   |     |                                                                                     |
| CHX 2%: 70.4/76              |                                                                   |     |                                                                                     |
| EDTA 0.5 m: 66.1/73.4        |                                                                   |     |                                                                                     |
| SE control                   |                                                                   |     |                                                                                     |
| E&R control                  |                                                                   |     |                                                                                     |
| Abb Nawareg et al. [23]      |                                                                   |     |                                                                                     |
| Group: immediate/6 m/12 m     |                                                                   |     |                                                                                     |
| CHX 2%: 93.3/86.7/86.7       |                                                                   | 36  |                                                                                     |
| CHX-MA 2%: 86.7/100/80       |                                                                   |     |                                                                                     |
| Control: 93.3/100/86.7       |                                                                   |     |                                                                                     |
| E&R                          |                                                                   |     |                                                                                     |
| Abb Nawareg et al. [23]      |                                                                   |     |                                                                                     |
| Group: immediate/6 m/12 m     |                                                                   |     |                                                                                     |
| Experimental adhesive        |                                                                   | 36  |                                                                                     |
| GAL 5 μm: 77/77/59           |                                                                   |     |                                                                                     |
| BAT 5 μm: 71/71/84           |                                                                   |     |                                                                                     |
| GM1 5 μm: 72/72/57           |                                                                   |     |                                                                                     |
| CHX 2%: 70/72/63             |                                                                   |     |                                                                                     |
| Control: 79/75/83            |                                                                   |     |                                                                                     |
| Single Bond 2: 68/74/84      |                                                                   |     |                                                                                     |
| E&R                          |                                                                   | 18 m|                                                                                     |
| CHX 2%: 93.3/86.7/86.7       |                                                                   |     |                                                                                     |
| CHX-MA 2%: 86.7/100/80       |                                                                   |     |                                                                                     |
| Control: 93.3/100/86.7       |                                                                   |     |                                                                                     |
| Montagner et al. [25]        |                                                                   |     |                                                                                     |
| NA                           |                                                                   | 36  |                                                                                     |
| NaOCl                        |                                                                   | 20.6|                                                                                     |
| Control                       |                                                                   | 44.6|                                                                                     |
| Sabatini et al. [26]         |                                                                   |     |                                                                                     |
| NA                           |                                                                   | 25  |                                                                                     |
| E&R                          |                                                                   | 1.3*|                                                                                     |
| CHX 2%: 93.3/86.7/86.7       |                                                                   |     |                                                                                     |
| BAC-PA 1%: 86.7/100/80       |                                                                   |     |                                                                                     |
| BAC 0.5%: 86.7/100/80        |                                                                   |     |                                                                                     |
| BAC 1%: 86.7/100/80          |                                                                   |     |                                                                                     |
| Control                       |                                                                   | 53.2|                                                                                     |
| Sabatini and Pashley [27]    |                                                                   |     |                                                                                     |
| NA                           |                                                                   | 35  |                                                                                     |
| E&R                          |                                                                   | 0.5%|                                                                                     |
| 0.5% BAC: 2.6*/1.6*          |                                                                   |     |                                                                                     |
| 2.0% BAC: 8.0*/7.0*          |                                                                   |     |                                                                                     |
| 0.5% MBAC: 11.2*/26.4*       |                                                                   |     |                                                                                     |
| 1.0% MBAC: 5.4*/23.1*        |                                                                   |     |                                                                                     |
| 2.0% MBAC: 6.5*/1.0*         |                                                                   |     |                                                                                     |
| Control                       |                                                                   | 44.2|                                                                                     |
| André et al. [28]            |                                                                   |     |                                                                                     |
| NA                           |                                                                   | 60  |                                                                                     |
| E&R                          |                                                                   | 5.8 |                                                                                     |
| GD                           |                                                                   | 32.1|                                                                                     |
| GD-control                   |                                                                   | 8.9 |                                                                                     |
| MDPB                         |                                                                   | 19.2|                                                                                     |
| MDPB-control                 |                                                                   | 2.5 |                                                                                     |
| 0.2% CHX-control             |                                                                   | 0.5%|                                                                                     |
| Article | Adhesive/mixed failure modes (%) in groups immediately/after aging | Technique of bonding (E&R/SE) | MMP inhibitor +% | Bond strength reduction (%) after aging |
|---------|---------------------------------------------------------------|-------------------------------|-----------------|-----------------------------------------|
|         |                                                               |                               |                 | 6m | 12m | >12 m |
| Manso et al. [29] | Group: immediate/6m/15m All-Bond 3® | E&R | - | 15 m |       |
|         | CHX 1% W: 73.5/51.6/58.3 Control W: 50/44.5/50 | CHX 1% water: -7.9 | - | 1.9 | 7.4 |
|         | Control E: 56.8/62.7/54.1 | Control ethanol: 5.1 | - | 25.3 |       |
|         | CHX 1% E: 75/55.8/65.3 | CHX 1% ethanol: 4.6 | - | 27.6 |       |
| Ekambaram et al. [30] | Group: immediate/12m Sound dentin EWB+CHX: 93.7/75 EWB control: 100/68.8 WWB control: 93.8/100 | EWB+CHX 2% 4.9 | - | 6.0 |       |
|         | EWB control: 100/68.8 WWB control: 100/10 | EWB control 21.2 | - | 27.1 |       |
|         | WWB control: 93.8/100 Caries-affected dentin EWB+CHX: 68.8/81.2 EWB control: 75.5/62.6 WWB control: 50/100 | WWB control 27.6 | - |       |       |
|         | WWB control: 56.3/62.5 | WWB control 6.4 | - | 14.4 |       |
| Sabatini and Patel [31] | Group: immediate/6m/18m OptiBond Solo Plus® | E&R | - | 18 m |       |
|         | 2% CHX: 70/70/60 BAC-PA: 60/60/60 0.25% BAC: 60/70/60 0.5% BAC: 70/70/60 1.0% BAC: 70/70/60 2.0% BAC: 70/70/60 All-Bond 3® | 2% CHX: 12.4 | - | 6.0 |       |
|         | 2% CHX: 70/70/60 BAC-PA: 60/60/60 0.25% BAC: 60/70/60 0.5% BAC: 70/70/60 1.0% BAC: 70/70/60 2.0% BAC: 70/70/60 All-Bond 3® | BAC-PA: -4.7 | - | -27.1 |       |
|         | 2% CHX: 70/70/60 BAC-PA: 60/60/60 0.25% BAC: 60/70/60 0.5% BAC: 70/70/60 1.0% BAC: 70/70/60 2.0% BAC: 70/70/60 All-Bond 3® | 0.25% BAC: 32.4 | - | 30.9 |       |
|         | 2% CHX: 70/70/60 BAC-PA: 60/60/60 0.25% BAC: 60/70/60 0.5% BAC: 70/70/60 1.0% BAC: 70/70/60 2.0% BAC: 70/70/60 All-Bond 3® | 0.5% BAC: 1.8 | - | -95.0 |       |
|         | 2% CHX: 70/70/60 BAC-PA: 60/60/60 0.25% BAC: 60/70/60 0.5% BAC: 70/70/60 1.0% BAC: 70/70/60 2.0% BAC: 70/70/60 All-Bond 3® | 1.0% BAC: -21.2 | - | -46.3 |       |
|         | 2% CHX: 70/70/60 BAC-PA: 60/60/60 0.25% BAC: 60/70/60 0.5% BAC: 70/70/60 1.0% BAC: 70/70/60 2.0% BAC: 70/70/60 All-Bond 3® | 2.0% BAC: 15.7 | - | -19.1 |       |
| Pomacóndor-Hernández et al. [32] | NA | E&R Solobond M® | CHX 2%: -8.1 | - | 2.7 |       |
|         | 8 | Control 2 |       |       |       |       |
| Verma et al. [33] | NA | Tetric N Bond® | CHX 2%: 0.9 | - | 0.7 |       |
|         | 120 | PAC 30%: 6.8 | - | 36.2 |       |       |
| Tjäderhane et al. [34] | NA | DMSO 0.5 mm | DMSO 0.5 mm: -15.7 | - | -36.4 |       |
|         | 20 | Control 37.2 | - | 30.4 |       |       |

* indicates a statistically significant difference.
| Article                  | Adhesive/mixed failure modes (%) in groups immediately/after aging | N   | Technique of bonding (E&R/SE) MMP inhibitor +% | Bond strength reduction (%) after aging |
|-------------------------|-------------------------------------------------------------------|-----|-----------------------------------------------|----------------------------------------|
|                         |                                                                   |     | Technique of bonding (E&R/SE) MMP inhibitor +% | 6 m  | 12 m  | >12 m |
| Sabatini et al. [35]    | Group: immediate/6m                                               | 25  | E&R                                          | 10.4* |
|                         | CHX 2%: 70/60                                                     |     | CHX 2%                                       |      |
|                         | BAC 0.5%: 80/80                                                   |     | BAC 1% PA                                    | 18.4*|
|                         | BAC 0.5%-adhesive: 70/80                                          |     | BAC 0.5%-adhesive                            | −0.5*|
|                         | Control: 70/60                                                    |     | Control                                      | 20.1 |
| Simoes et al. [36]      | NA                                                                | 36  | E&R                                          | 28.5 |
|                         | CHX                                                               |     | Control                                      | 32.7 |
|                         | CHX + ethanol                                                    |     | CHX + ethanol                                | 21.4 |
|                         | Ethanol control                                                  |     | Ethanol control                              | 7.6  |
| Sabatini [37]           | Group: immediate/6m                                               | 120 | E&R                                          |      |
|                         | CHX 2% + 0.2% CHX-adhesive: 70/50                                 |     | CHX 2% + 0.2% CHX-adhesive                   | −4.2 |
|                         | 0.2%-adhesive: 80/60                                              |     | 0.2% CHX-adhesive                            | 5.2  |
|                         | Control: 90/70                                                    |     | Control                                      | −14.3|
|                         | SE                                                                |     | SE                                           |      |
|                         | CHX 2% + 0.2% CHX-adhesive: 60/60                                 |     | CHX 2% + 0.2% CHX-adhesive                   | −13.8|
|                         | 0.2% CHX-adhesive: 50/80                                          |     | 0.2% CHX-adhesive                            | −17.4|
|                         | Control: 60/80                                                    |     | Control                                      | −6.3 |
| Ali et al. [38]         | NA                                                                | 30  | E&R                                          |      |
|                         | 2% CHX-ethanol                                                   |     | 2% CHX-ethanol                               | 64.2*|
|                         | 2% CHX-dH₂O                                                      |     | 2% CHX-dH₂O                                  | −13.8|
|                         | Control                                                          |     | Control                                      | 36.5 |
| Leitune et al. [39]     | NA                                                                | 40  | E&R                                          |      |
|                         | CHX 2%                                                           |     | CHX 2%                                       | −9.8*|
|                         | Control                                                          |     | Control                                      | 10.9 |
| Cova et al. [40]        | Group: immediate/6 m/12 m                                         | 60  | E&R                                          |      |
|                         | RF 0.1%: 98/95/97                                                 |     | RF 0.1%                                      | 19.8*|
|                         | Control: 89/89/95                                                 |     | Control                                      | 41.0 |
|                         | SE                                                                |     |                                             | 24 m |
|                         | CHX 2%                                                           |     |                                              | ND 63.3 AD 52.1|
|                         | CHX 5%                                                           |     |                                              | ND 57.7 AD 28.8*|
|                         | Control                                                          |     |                                              | ND 61.1 AD 54.1|
| Mobarak [41]            | NA                                                                | 120 | E&R                                          |      |
|                         | CHX 2%                                                           |     |                                             |      |
|                         | Control                                                          |     |                                             |      |
| Sadek et al. [42]       | NA                                                                | 42  | E&R                                          |      |
|                         | CHX 2%                                                           |     |                                             |      |
|                         | Control                                                          |     |                                             |      |
|                         | CHX 2%                                                           |     |                                             |      |
|                         | Control                                                          |     |                                             |      |
|                         | CHX 2%                                                           |     |                                             |      |
|                         | Control                                                          |     |                                             |      |

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| Article            | Adhesive/mixed failure modes (%) in groups immediately/after aging | N  | Technique of bonding (E&R/SE) MMP inhibitor + % | Bond strength reduction (%) after aging |
|-------------------|---------------------------------------------------------------|----|-------------------------------------------------|----------------------------------------|
|                   |                                                               |    | E&R Prime & Bond NT®                             |                                        |
|                   |                                                               |    | Control                                         |                                        |
| Stanislawczuk et al. [43] | NA                                          | 42 | CHX                                             | 24 m                                   |
|                   |                                                               |    | CHX-PA                                          | 53.5                                   |
|                   |                                                               |    | CHX                                             | 19.2*                                  |
| De Munck et al. [44] | Group: Immediate/6 m/12 m                                     | 45 | E&R Adper Single Bond®                          |                                        |
|                   |                                                               |    | Control                                         |                                        |
|                   |                                                               |    | CHX                                             | 46.9                                   |
|                   |                                                               |    | CHX-PA                                          | 18.9*                                  |
|                   |                                                               |    | CHX-PA                                          | 16.3*                                  |
| Ricci et al. [45]  | Group: immediate/10–12 m/18–20 m                              | 26 | E&R                                             |                                        |
|                   |                                                               |    | E&R                                             | 10–12 m                                |
|                   |                                                               |    | CHX                                             | 26.3                                   |
| Breschi et al. [46] | Group: immediate/12 m                                         | 28 | E&R                                             | 18–20 m                                |
|                   |                                                               |    | GAL 0.04%                                       | 37.0*                                  |
| Breschi et al. [47] | Group: immediate/24 m                                         | 48 | E&R                                             |                                        |
|                   |                                                               |    | Control                                         |                                        |
| Loguercio et al. [48] | Group: immediate/6 m                                          | 120| E&R                                             |                                        |
|                   |                                                               |    | Control                                         |                                        |
| Stanislawczuk et al. [49] | Group: immediate/6 m                                          | 42 | E&R                                             |                                        |
|                   |                                                               |    | Control                                         |                                        |
|                   |                                                               |    | CHX                                             | 16*                                    |
|                   |                                                               |    | CHX-PA                                          | 4.6*                                   |
Table 1: Continued.

| Article               | Adhesive/mixed failure modes (%) in groups immediately/after aging | Technique of bonding (E&R/SE) MMP inhibitor + % | Bond strength reduction (%) after aging |
|-----------------------|---------------------------------------------------------------|-----------------------------------------------|---------------------------------------|
|                       |                                                               |                                               | 6m  | 12m  | >12m |
| Group: immediate/12m  |                                                               |                                               |     |      |      |
| Zhou et al. [50]      |                                                               |                                               |     |      |      |
| Control: 93.8/100     | 0.05% CHX: 93.8/100                                           | 0.05% CHX                                     | 18.1|
| Control: 87.5/93.8    | 0.1% CHX: 75/93.8                                             | 0.1% CHX                                      | 18.7|
| Control: 93.8/100     | 0.5% CHX: 87.5/100                                            | 0.5% CHX                                      | −0.8*|
| Control: 93.8/100     | 1% CHX/93.8/93.8                                              | 1% CHX                                        | 2.9* |
| Control: 87.5/100     |                                                               | Control                                       | 15.6|
| Group: immediate/12m  |                                                               |                                               |     |      |      |
| Breschi et al. [51]   |                                                               |                                               |     |      |      |
| Control: 100/90/90    | CHX 2%: 90/95/95                                               | 2%                                            | 11  | 24.6*|
| Control: 100/90/90    | CHX 0.2%: 100/95/100                                          | 0.2%                                          | 16.5| 20.8*|
| Control: 100/90/90    | CHX 0.2%: 95/100/85                                           | 0.2%                                          | 13.1| 30.8*|
| Control: 100/90/90    |                                                               | Control                                       | 33.1| 64.1 |

Figure 2: Forest plot of studies at baseline. The N for both groups was 396 samples. The total random effect standardized mean difference (SMD) was −0.0821 (CI 95% −0.240; 0.076). The difference was not statistically significant (t = −1.019, P = 0.308). The I² (inconsistency) was 21.68%.
(a) Favors control  Favors CHX
Standardized
mean difference

(b) Favors control  Favors CHX
Standardized
mean difference

Figure 3: Continued.
Table 2: Factors associated with the risk of bias in different studies.

| Study                        | Materials | Caries | Adhesive | Sample | Blinding | Random | Risk |
|------------------------------|-----------|--------|----------|--------|----------|--------|------|
| Ou et al. [11]               | Y         | Y      | NM       | NM     | NM       | NM     | Y    | Medium |
| Giacomini et al. [14]        | Y         | Y      | NM       | NM     | NM       | NM     | NM   | High   |
| Daood et al. [15]            | Y         | Y      | NM       | NM     | NM       | Y      | Y    | Medium |
| Carvalho et al. [17]         | NM        | N      | Y        | NM     | NM       | Y      | High |
| Abu Nawareg et al. [23]      | Y         | Y      | NM       | NM     | NM       | N      | Y    | Medium |
| Loguercio et al. [20]        | Y         | Y      | Y        | NM     | NM       | Y      | Medium |
| Tekçe et al. [22]            | Y         | Y      | NM       | NM     | NM       | Y      | Y    | Medium |
| Montagner et al. [25]        | Y         | Y      | Y        | NM     | NM       | Y      | Y    | Medium |
| Ekambaram et al. [30]        | NM        | Y      | NM       | NM     | NM       | Y      | High |
| Sabatini et al. [31]         | Y         | Y      | NM       | NM     | NM       | Y      | Medium |
| Verma et al. [33]            | NM        | Y      | NM       | NM     | NM       | Y      | High |
| Sabatini et al. [35]         | Y         | Y      | NM       | NM     | NM       | Y      | Medium |
| Sabatini [37]                | Y         | Y      | NM       | NM     | NM       | Y      | Y    | Medium |
| Leitune et al. [39]          | Y         | Y      | NM       | NM     | NM       | Y      | Y    | Medium |
| Stanislawczuk et al. [43]    | NM        | Y      | Y        | NM     | NM       | NM     | NM   | High   |
| Sadek et al. [42]            | Y         | Y      | NM       | NM     | NM       | Y      | Medium |
| Ricci et al. [45]            | Y         | N      | Y        | NM     | NM       | Y      | Medium |
| Loguercio et al. [48]        | Y         | Y      | Y        | NM     | NM       | Y      | Medium |
| Stanislawczuk et al. [49]    | NM        | Y      | Y        | NM     | NM       | NM     | NM   | High   |
| Breschi et al. et al. [51]   | Y         | Y      | NM       | NM     | NM       | Y      | Medium |
| Loguercio et al. [48]        | Y         | Y      | Y        | NM     | NM       | Y      | Medium |

Total 21

16 19 8 0 0 18
both [2, 6]. This supports the idea that bond strength decreases over time and that the adhesive interface plays a significant role in the mode of fracture.

A thorough risk of bias assessment was also carried out to identify the main factors which could affect the credibility of the findings. Five articles were classified to have a high risk of bias, and none with low risk. The results are in line with the respective previous study [8]. None of the studies mentioned sample size calculations, and all but one failed to mention the blinding of the operator performing the bond strength testing. The results may reflect the standard level of reporting of bond strength studies, but at least the blinding of the person performing the bond strength testing should be done and also reported.

5. Conclusions

This systematic review and meta-analysis demonstrated that studies strongly indicate the benefits of collagen-degrading enzyme inhibition on the preservation of dentin bond strength. Since CHX does not have any adverse effects on the immediate bond strength, the clinical use of CHX can be recommended to increase the longevity of resin-dentin bonds.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Kiuru O. and Sinervo J, the first two authors, had an equal contribution to the article.

References

[1] M. Hashimoto, H. Ohno, M. Kaga, K. Endo, H. Sano, and H. Oguchi, “In vivo degradation of resin-dentin bonds in humans over 1 to 3 years,” Journal of Dental Research, vol. 79, no. 6, pp. 1385–1391, 2000.
[2] L. Tjäderhane, F. D. Nascimento, L. Breschi et al., “Optimizing dentin bond durability: control of collagen degradation by matrix metalloproteinases and cysteine cathepsins,” Dental Materials, vol. 29, no. 1, pp. 116–135, 2013.
[3] D. H. Pashley, F. R. Tay, L. Breschi et al., “State of the art etch-and-rinse adhesives,” Dental Materials, vol. 27, no. 1, pp. 1–16, 2011.
[4] B. Van Meerbeek, K. Yoshihara, Y. Yoshida, A. Mine, J. De Munck, and K. L. Van Landuyt, “State of the art of self-etch adhesives,” Dental Materials, vol. 27, no. 1, pp. 17–28, 2011.
[5] F. M. Collares, S. B. Rodrigues, V. C. Leitune, R. K. Celeste, F. Borba de Araujo, and S. M. Samuel, “Chlorhexidine application in adhesive procedures: a meta-regression analysis,” The Journal of Adhesive Dentistry, vol. 15, no. 1, pp. 11–18, 2013.
[6] A. Mazzoni, L. Tjäderhane, V. Checchi et al., “Role of dentin MMPs in caries progression and bond stability,” Journal of Dental Research, vol. 94, no. 2, pp. 241–251, 2015.
[7] A. K. Bedran-Russo, G. F. Pauli, S.-N. Chen et al., “Dentin biomodification: strategies, renewable resources and clinical applications,” Dental Materials, vol. 30, no. 1, pp. 62–76, 2014.
[8] A. F. Montagner, R. Sarkis-Onofre, T. Pereira-Cenci, and M. S. Cenci, “MMP inhibitors on dentin stability,” Journal of Dental Research, vol. 93, no. 8, pp. 733–743, 2014.
[9] J. Li, B. Chen, N. Hong, S. Wu, and Y. Li, “Effect of baicalein on matrix metalloproteinases and durability of resin-dentin bonding,” Operative Dentistry, vol. 43, no. 4, pp. 426–436, 2018.
[10] P. Malaquias, M. Gutierrez, V. Hass et al., “Two year effects of chlorhexidine-containing adhesives on the in vitro durability of resin-dentin interfaces and modeling of drug release,” Operative Dentistry, vol. 43, no. 2, pp. 201–212, 2018.
[11] Q. Ou, Y. Hu, S. Yao, Y. Wang, and X. Lin, “Effect of matrix metalloproteinase 8 inhibitor on resin-dentin bonds,” Dental Materials, vol. 34, no. 5, pp. 756–763, 2018.
[12] M. El Gezawi, R. Hardiy, E. Abo Elazm, F. Al-Harbi, M. Zouch, and D. Kaisarly, “Microtensile bond strength, 4-point bending and nanoleakage of resin-dentin interfaces: effects of two matrix metalloproteinase inhibitors,” Journal of the Mechanical Behavior of Biomedical Materials, vol. 78, pp. 206–213, 2018.
[13] T. Maravic, L. Breschi, A. Comba et al., “Experimental use of an acrolein-based primer as collagen cross-linker for dentine bonding,” Journal of Dentistry, vol. 68, pp. 85–90, 2018.
[14] M. Giacomini, P. Scaffa, L. Chaves et al., “Role of proteolytic enzyme inhibitors on carious and eroded dentin associated with a universal bonding system,” Operative Dentistry, vol. 42, no. 6, pp. E188–E196, 2017.
[15] D. Daoed, C. K. Y. Yiu, M. F. Burrow, L.-N. Niu, and F. R. Tay, “Effect of a novel quaternary ammonium silane cavity disinfectant on durability of resin-dentine bond,” Journal of Dentistry, vol. 60, pp. 77–86, 2017.
[16] B. Venigalla, P. Jyothi, S. Kamishetty, S. Reddy, R. Cherukupalli, and D. Reddy, “Resin bond strength to water versus ethanol-saturated human dentin pretreated with three different cross-linking agents,” Journal of Conservative Dentistry, vol. 19, no. 6, pp. 555–559, 2016.
[17] C. Carvalho, F. P. Fernandes, V. D. P. Freitas et al., “Effect of green tea extract on bonding durability of an etch-and-rinse adhesive system to caries-affected dentin,” Journal of Applied Oral Science, vol. 24, no. 3, pp. 211–217, 2016.
[18] D. C. Barcellos, B. M. Fonseca, C. R. Pucci, B. D. N. Cavalcanti, E. D. S. Persici, and S. E. D. P. Gonçalves, “Zn-doped etch-and-rinse model dentin adhesives: dentin bond integrity, biocompatibility, and properties,” Dental Materials, vol. 32, no. 7, pp. 940–950, 2016.
[19] V. Hass, I. V. Luque-Martinez, M. F. Gutierrez et al., “Collagen cross-linkers on dentin bonding: stability of the adhesive interfaces, degree of conversion of the adhesive, cytotoxicity and in situ MMP inhibition,” Dental Materials, vol. 32, no. 6, pp. 732–741, 2016.
[20] A. Loguercio, R. Stasiñawczuk, P. Malaquias, M. Gutierrez, J. Bauer, and A. Reis, “Effect of minocycline on the durability of dentin bonding produced with etch-and-rinse adhesives,” Operative Dentistry, vol. 41, no. 5, pp. 511–519, 2016.
[21] V. Hass, I. Luque-Martinez, M. A. Muñoz et al., “The effect of proanthocyanidin-containing 10% phosphoric acid on bonding properties and,” MMP Inhibition Dental Materials, vol. 32, no. 3, pp. 468–475, 2016.
and in situ study,” Operative Dentistry, vol. 39, no. 1, pp. 64–71, 2014.

C. Sabatini, “Effect of a chlorhexidine-containing adhesive on dentin bond strength stability,” Operative Dentistry, vol. 38, no. 6, pp. 609–617, 2013.

A. Ali, H. El Deeb, O. Badran, and E. Mobarak, “Bond durability of self-etch adhesive to ethanol-based chlorhexidine pretreated dentin after storage in artificial saliva and under intrapulpal pressure simulation,” Operative Dentistry, vol. 38, no. 4, pp. 439–446, 2013.

V. C. B. Leitune, F. F. Portella, P. V. Bohn, F. M. Collares, and S. M. W. Samuel, “Influence of chlorhexidine application on longitudinal adhesive bond strength in deciduous teeth,” Brazilian Oral Research, vol. 25, no. 5, pp. 388–392, 2011.

A. Cova, L. Breschi, F. Nato et al., “Effect of UVA-activated riboflavin on dentin bonding,” Journal of Dental Research, vol. 90, no. 12, pp. 1439–1445, 2011.

E. Mobarak, “Effect of chlorhexidine pretreatment on bond strength durability of caries-affected dentin over 2 year aging in artificial saliva and under simulated intrapulpal pressure,” Operative Dentistry, vol. 36, no. 6, pp. 649–660, 2011.

F. T. Sadek, R. R. Braga, A. Muench, Y. Liu, D. H. Pashley, and F. R. Tay, “Ethanol wet-bonding challenges current anti-degradation strategy,” Journal of Dental Research, vol. 89, no. 12, pp. 1499–1504, 2010.

R. Stanisławczuk, A. Reis, and A. D. Loguercio, “A 2 year in vitro evaluation of a chlorhexidine-containing acid on the durability of resin-dentin interfaces,” Journal of Dentistry, vol. 39, no. 1, pp. 40–47, 2011.

J. De Munck, A. Mine, P. E. Van den Steen et al., “Enzymatic degradation of adhesive-dentin interfaces produced by mild self-etch adhesives,” European Journal of Oral Sciences, vol. 118, no. 5, pp. 494–501, 2010.

H. A. Ricci, M. E. Sanabe, C. A. de Souza Costa, D. H. Pashley, and J. Hebling, “Chlorhexidine increases the longevity of in vivo resin-dentin bonds,” European Journal of Oral Sciences, vol. 118, no. 4, pp. 411–416, 2010.

L. Breschi, P. Martin, A. Mazzoni et al., “Use of a specific MMP-inhibitor (galardin) for preservation of hybrid layer,” Dental Materials, vol. 26, no. 6, pp. 571–578, 2010.

L. Breschi, A. Mazzoni, F. Nato et al., “Chlorhexidine stabilizes the adhesive interface: a 2 year in vitro study,” Dental Materials, vol. 26, no. 4, pp. 320–325, 2010.

A. D. Loguercio, R. Stanisławczuk, L. G. Polli, J. A. Costa, M. D. Michel, and A. Reis, “Influence of chlorhexidine digluconate concentration and application time on resin-dentin bond strength durability,” European Journal of Oral Sciences, vol. 117, no. 5, pp. 587–596, 2009.

R. Stanisławczuk, R. C. Amaral, C. Zander-Grande, D. Gagler, A. Reis, and A. D. Loguercio, “Chlorhexidine-containing acid conditioner preserves the longevity of resin-dentin bonds,” Operative Dentistry, vol. 34, no. 4, pp. 481–490, 2009.

J. Zhou, J. Tan, L. Chen, D. Li, and Y. Tan, “The incorporation of chlorhexidine in a two-step self-etching adhesive preserves dentin bond in vitro,” Journal of Dentistry, vol. 37, no. 10, pp. 807–812, 2009.

L. Breschi, F. Cammelli, E. Visintini et al., “Influence of chlorhexidine concentration on the durability of etch-and-rinse dentin bonds: a 12 month in vitro study,” The Journal of Adhesive Dentistry, vol. 11, no. 3, pp. 191–198, 2009.