https://doi.org/10.36377/ET-0071

Effect of dentin bio modifications and matrix metalloproteinase activity on bond strength – A systematic review and meta-analysis

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Abstract
AIM. To evaluate effect of dentin bio-modifications and matrix metalloproteinase (MMP) inhibitors on dentin bonding.
METHODS. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was registered in PROSPERO. A thorough search of Google scholar, Pubmed Central, EBSCO host was conducted from January 2000 to December 2023 to identify studies examining the impact of various dentin bio modifications and MMP inhibitors on dentin bonding. Quality assessment was performed using the Cochrane risk of bias (ROB) –2 tool for randomized controlled trials (RCTs), evaluating each study's domains through Review Manager (RevMan) software version 5.3. The standardized mean difference (SMD) served as the summary statistic measure, employing a random-effect model with a significance threshold set at $p < 0.05$.
RESULTS. Sixteen studies met the eligibility criteria and underwent qualitative synthesis, with fifteen studies in meta-analysis. Upon quality assessment, the studies demonstrated a range of moderate to low risk of bias. A variety of dentin modifiers and MMP inhibitors were included, of which 2% chlorhexidine and benzalkonium chloride being the most studied in twelve and five studies respectively. The pooled estimate through SMD suggested that 2% CHX 2.28 (–3.69–0.03) and BAC 2.50 (–7.80–2.79) had an overall greater dentin bonding compared to other control measures used.
CONCLUSION. It was concluded that biomodifiers and MMP inhibitors have a positive effect on the bond strength of adhesives. It was seen that 2% CHX and BAC had greater dentin bond strength.

Keywords: bond strength, chlorhexidine, dentin biomodification, matrix metalloproteinases

Article info: received – 05.09.2024; revised – 10.10.2024; accepted – 15.10.2024

Conflict of interests: The authors declare no conflict of interests.

Acknowledgments: There are no funding and individual acknowledgments to declare.

For citation: Agarwal D., Srinidhi S.R., Aggarwal S.D., Ingle P., Tandon S. Effect of dentin bio modifications and matrix metalloproteinase activity on bond strength – A systematic review and meta-analysis. *Endodontics Today*. 2025;23(1):71–79. https://doi.org/10.36377/ET-0071

Влияние биомодификации дентина и активности матриксных металлопротеиназ на прочность адгезии – систематический обзор и мета-анализ

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Резюме
ЦЕЛЬ. Оценить влияние биомодификаций дентина и ингибиторов матриксных металлопротеиназ (ММП) на адгезию к дентину.
МЕТОДЫ. Обзор выполнен в соответствии с рекомендациями PRISMA и зарегистрирован в PROSPERO. Был проведен тщательный поиск в базах данных Google Scholar, PubMed Central и EBSCO Host с января 2000 по декабрь 2023 г. для выявления исследований, оценивающих влияние различных биомодификаций дентина и ингибиторов ММП на адгезию к дентину. Оценка качества исследований проводилась с помощью инструмента Cochrane ROB-2 для рандомизированных контролируемых исследований (РКИ), а анализ был выполнен с использованием программы RevMan версии 5.3. В качестве статистической меры использовалась стандартизированная средняя разница (SMD) с моделью случайных эффектов при уровне значимости $p < 0.05$.
РЕЗУЛЬТАТЫ. Шестнадцать исследований соответствовали критериям отбора и были включены в качественный синтез, пятнадцать из них – в мета-анализ. При оценке качества исследований была об-

наружена умеренная и низкая степень риска смещения. Были исследованы различные модификаторы дентина и ингибиторы ММП, среди которых наиболее часто изучались 2% хлоргексидин (CHX) и бензалкония хлорид (BAC) в двенадцати и пяти исследованиях соответственно. По результатам мета-анализа, общая прочность адгезии дентина при использовании 2% CHX составила 2.28 (–3.69–0.03), а при использовании BAC – 2.50 (–7.80–2.79) по сравнению с другими контрольными мерами.
ВЫВОД. Биомодификаторы и ингибиторы ММП оказывают положительное влияние на прочность адгезии к дентину. Наибольшая прочность адгезии отмечена при использовании 2% CHX и BAC.

Ключевые слова: прочность адгезии, хлоргексидин, биомодификация дентина, матриксные металлопротеиназы

Информация о статье: поступила – 05.09.2024; исправлена – 10.10.2024; принята – 15.10.2024

Конфликт интересов: Авторы сообщают об отсутствии конфликта интересов.

Благодарности: Финансирование и индивидуальные благодарности для декларирования отсутствуют.

Для цитирования: Агарвал Д., Сринитхи С.Р., Агарвал Ш.Д., Ингле П., Тандон С. Влияние биомодификации дентина и активности матриксных металлопротеиназ на прочность адгезии – систематический обзор и мета-анализ. *Эндодонтия Today.* 2025;23(1):71–79. https://doi.org/10.36377/ET-0071

INTRODUCTION

The primary obstacle to the longevity of composite resin restorations lies in the intricate nature of dentin structure. The major constituent of dentin is Type – I fibrillar collagen which has the function of tissue protection and enhances adhesion by cross linking and makes the fibril resistant to degradation [1]. Current methods for restoring teeth involve the partial or complete infiltration of adhesive components into demineralized collagen fibres which comprises the organic matrix of dentin. Application of acid to dentin followed by resin adhesive results in the formation of a layer of resin-infiltrated collagen fibril network which was termed as the hybrid layer [2].

Many factors such as excessive monomer inclusion in the hydrophilic adhesive system, high water concentrations during the bonding process, insufficient monomer penetration for demineralized collagen may cause a decrease in dentin adhesion and deterioration of the hybrid layer [3]. Water penetration triggers the hydrolysis of monomers, failing to shield collagen fibres from degradation [4].

Unprotected and exposed collagen cells are susceptible to endogenous proteases like MMPS. Hence methods such as dentin biomodification and the use of MMP inhibitors have garnered increased attention to improve the durability of the bond between dentin and resin. This approach utilizes synthetic bio-modifiers or natural products which increase the ability to bind collagen fibres, thus improving biomechanics and reducing biodegradation [5].

Dentin bond strength deteriorates with the degradation of the hybrid layer. Acid exposure (in etch and rinse adhesives) or acidic monomers (in self-etch adhesives) leads to demineralization of the dentin collagen matrix, facilitating integration with the adhesive. Extensive studies have explored MMP inhibitors such as chlorhexidine, galatine and benzalkonium chloride for their potential to inhibit these enzymes. Additionally, collagen cross linkers have emerged as a promising agent for inhibiting proteases [6].

Very few studies have offered a thorough quantitative and comparative assessment of the impact of different dentin modifications and MMP inhibitors on dentin bonding. Thus, null hypothesis for this study can be postulated as “there will be no effect of the biomodifiers and MMP inhibitors on the dentin bond strength”.

MATERIALS AND METHODS

Protocol development

Review was adhered to PRISMA 2020 guidelines [7] and Prospective Registration of Systematic Reviews (PROSPERO) – CRD42023454259 registration was done.

Study design

The research question “What is the effect of dentin bio-modifications on dentin bonding and MMP activity?” was put out in the Participants (P), Intervention (I), Comparison (C) and Outcome (O) framework:

P – dentin;
I – dentin biomodifiers and MMP inhibitors;
C – no comparison;
O – bond strength.

Eligibility Criteria

A) Inclusion Criteria:

1) articles published in open access journals in English;

2) studies published between January 2000 – December 2023 and having relevant data on the effect of various dentin bio-modifications on dentin bonding and MMP activity;

3) studies reporting the data in terms of mean, standard deviation and frequency;

4) comparative studies, in vitro studies, randomized controlled trials were included.

B) Exclusion Criteria:

1) case reports, letters to editor, short communications articles in press and dissertations submitted to universities;

2) articles which cannot be translated to English language;

3) if full text articles are not available.

Screening Process

The process of choosing articles was divided into two phases. Two reviewers, (DA, SR) looked over the titles and abstracts of every article in first round. Articles that did not fit into the inclusion were removed. Phase-two involved independent screening and review of full papers by the same reviewers. Discussions were held to settle any disputes. A third reviewer (SA) was brought in to screen through the entire search to remove any risk of biases.

Search Strategy

For research published within last 23 years (from 2000 to 2023), an electronic search was carried out till December 2023 utilizing the following databases: PubMed, google scholar and EBSCO host to retrieve English language articles.

The proper Boolean operators like AND/OR were used and combined with Medical Subject Heading (MeSH) terms. The keywords and their combinations: ''(Dentin AND bonding) OR (grape seed extract AND dentin AND bonding) OR chlorhexidine OR "benzalkonium chloride*" OR "matrix metalloproteinase inhibitor*" OR "MMP* inhibitor" OR "protease inhibitor") OR stability OR durability OR strength OR long-term) AND (dentin AND adhesive OR adhesive system" OR "hybrid layer*" OR bond OR ("matrix metalloproteinase" OR "MMP*inhibitor*") AND bond strength OR (("Matrix Metalloproteinase Inhibitors") AND ("Dental Bonding").

Data extraction

For all included studies, the following headings were included in the final analysis: author(s), country of study, year of study, sample size, study design, bio-modifiers and MMP inhibitors and bonding type (Etch and Rinse / Self-Etched)

Evaluation of methodological quality

The methodological quality of included studies was executed through Cochrane collaboration risk of bias (ROB) -2 tool [8] through its various domains in Review Manager (RevMan) 5.3 software.

Statistical analysis

Statistical analysis was conducted using RevMan 5.3 with standardized mean difference (SMD) serving as the summary measure. Significance was determined at the threshold of $p < 0.05$.

Assessment of heterogeneity

The Cochrane test for heterogeneity was employed to assess the significance of any differences in treatment effect estimations among trials. Heterogeneity was deemed statistically significant if the p-value was <0.01.

Investigation of publication bias

The study assessed publication bias using Begg's funnel plot, which plots the effect size against standard error. Asymmetry in the funnel plot which indicates potential publication bias was not seen in this review.

RESULTS

Study Characteristics

According to PRISMA 2020 guidelines (Fig. 1), data was evaluated from sixteen studies [9–24] subjected to dentin bio-modifiers and MMP inhibitors. All the included studies had in-vitro or clinical trial study design. Among the included studies, four studies were conducted in Iran [9; 10; 22; 23], three studies in Turkey [11; 20; 24], one in India [13], two in Egypt [14; 16], two in Saudi Arabia [15; 21], one in Portugal [17], two in Italy [12; 19] and one in Sweden [18]. The effect of bio-modifiers and MMP inhibitors like 1% BAC and 2% CHX on increasing the dentin bonding or adhesion of various adhesive materials has been described with the type of bonding done (Table 1).

Evaluation of methodological quality

The greatest risk of bias (ROB) was observed in random sequence generation, blinding of participants and personnel, blinding of outcome assessment, and selective reporting. However, all the studies included in the analysis reported moderate to the lowest levels of ROB overall. Domains such as incomplete outcome data, blinding of outcome assessment, and other biases were assigned the lowest levels of ROB. Detailed assessments of ROB across various domains and individual studies are visually represented. (Fig. 2, 3)

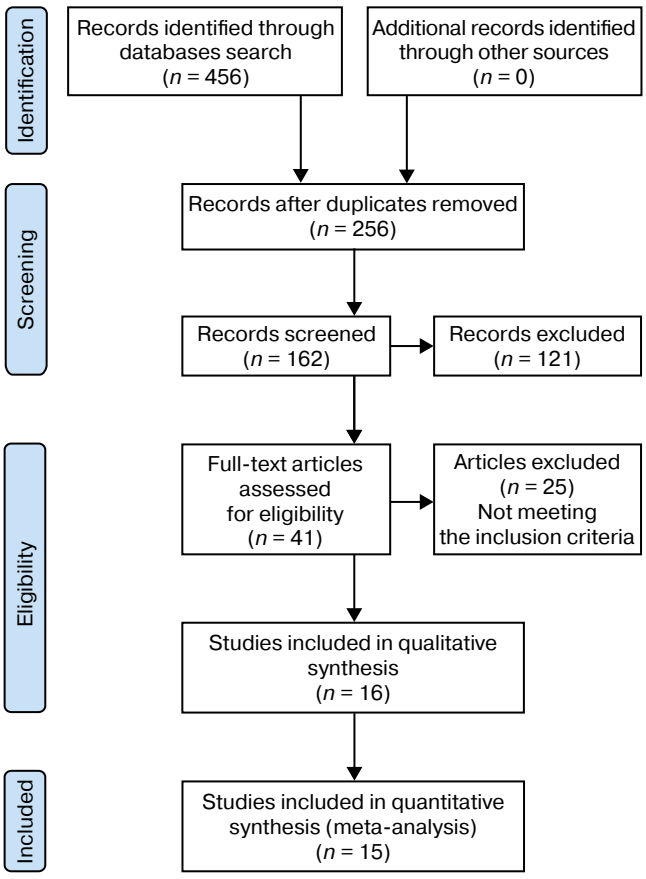

Fig. 1. PRISMA Flow Diagram

Рис. 1. Блок-схема PRISMA

Table 1. Descriptive study details of included studies

Таблица 1. Описание характеристик включенных исследований

Author, years of study	Country	Study design	Sample size	Biomodifiers and MMP inhibitors	Bonding type (E&R / SE)
Leitune et al., 2011 [9]	Iran	In-vitro clinical study	40	CHX 2% and control	E&R
Mobarak et al., 2011 [10]	Iran	In-vitro clinical study	120	CHX 2%, 5% and control	SE
Pomacóndor- Hernández et al., 2013 [11]	Turkey	In-vitro clinical study	8	CHX 2% and control	SE
Sabatini et al., 2013 [12]	Italy	In-vitro clinical study	25	CHX 2%, BAC 1%, control	E&R
Verma et al., 2013 [13]	India	In-vitro clinical study	20	CHX 2%, PAC 30% and control	E&R
Sabatini et al., 2014 [14]	Egypt	In-vitro clinical study	140	CHX 2%, BAC-PA, 0.25% BAC, 0.5%, 1%, 2% BAC and control	E&R
Montagner et al., 2015 [15]	Saudi Arabia	In-vitro clinical study	36	CHX 2%, NaOCL and control	E&R
Sabatini et al., 2015 [16]	Egypt	In-vitro clinical study	25	CHX 2%, BAC-PA 1%, BAC 0.5%, BAC 1% and control	E&R
Carvalho et al., 2016 [17]	Portugal	In-vitro clinical study	30	Green tea 2%, CHX 2% and control	E&R
Loguercio et al., 2016 [18]	Sweden	In-vitro clinical study	30	MC 2%, CHX 2%, control	E&R
Nawareg et al., 2016 [19]	Italy	In-vitro clinical study	36	CHX 2%, CHX-MA 2% and control	E&R
Tekçe et al., 2016 [20]	Turkey	In-vitro clinical study	50	BAC 1%, CHX 2%, EDTA 0.5 m	E&R and SE
Daood et al., 2017 [21]	Saudi Arabia	In-vitro clinical study	60	CHX 2%, QAS 2%, 5%,10% and control	E&R
Giacomini et al., 2017 [22]	Iran	In-vitro clinical study	90	CHX 2%, E-64 and control	E&R
El Gezawi et al., 2018 [23]	Iran	In-vitro clinical study	36	MDPB, BAC and control	SE
Malaquias et al., 2018 [24]	Turkey	In-vitro clinical study	50	CHX0 0.01%, 0.05%, 0.1%, 0.2% and control	E&R

Note: BAC – benzalkonium chloride; CHX – chlorhexidine; E&C – etch and rinse; EDTA – ethylene dioxide tri-aggregate; SE – self-etch; MDPB – methacrolxydodecylpyridium bromide; PAC – pro-anthocyanidines; QAS –quaternary ammonium silane.

Примечания: BAC – бензалкония хлорид; CHX – хлоргексидин; E&C – протравливание и смывание; EDTA – триагрегат этиленоксида; SE – самопротравливающий; MDPB – метакролоксидодецилпиридиния бромид; PAC – проантоцианидины; QAS – четвертичный аммониевый силан.

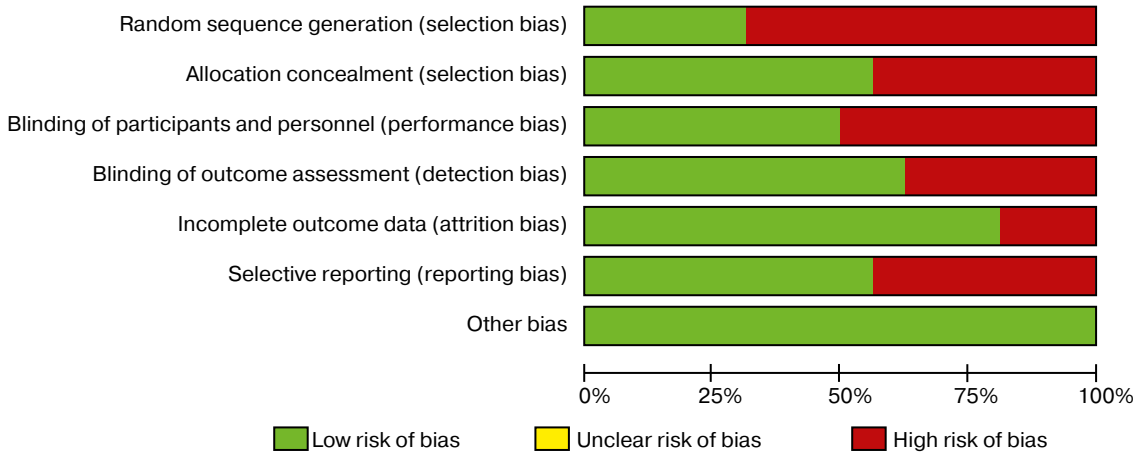

Fig. 2. Risk of Bias of selected studies

Рис. 2. Риск систематической ошибки в выбранных исследованиях

Synthesis of results

The meta-analysis was performed to evaluate the effect of CHX and BAC on MMP inhibition and on dentin bonding are shown in Fig. 4 and 5.

A) Effect of 2% CHX as a MMP inhibitor on dentin bonding

Twelve studies [10–22] containing data on 1470 teeth, of which (n=735) teeth were evaluated by CHX 2% group and (n=735) teeth by control group for the evaluation of the better effectiveness in terms of MMP inhibition and greater dentin bonding.

As shown in Fig. 4**,** the SMD is 2.28 (–3.69–0.03) and the pooled estimates favours CHX 2% group signifying that overall greater dentin bonding on an average is 2.28 times greater in 2% CHX group (p<0.05).

B) Effect of BAC as an MMP inhibitor and dentin bonding

Five studies [14; 16; 20; 23] containing data on 576 teeth, of which (n=288) teeth were evaluated by BAC group and (n=288) teeth by control group for the evaluation of the better effectiveness in terms of MMP inhibition and greater dentin bonding.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Carvalho et al., 2016 [17]	+	+	+	+	+	+	+
Daood et al., 2017 [21]	+	–	+	–	+	–	+
El Gezawi et al., 2018 [23]	–	+	–	+	–	+	+
Giacomini et al., 2017 [22]	+	+	–	–	+	–	+
Leitune et al., 2011 [9]	–	–	+	+	+	–	+
Loguercio et al., 2016 [18]	–	–	+	+	+	–	+
Malaquias et al., 2018 [24]	–	+	–	–	+	+	+
Mobarak et al., 2011 [10]	–	–	–	+	+	–	+
Montagner et al., 2015 [15]	+	+	+	+	+	+	+
Nawareg et al., 2016 [19]	–	–	+	–	–	+	+
Pomacóndor- Hernández et al., 2013 [11]	–	+	–	+	+	+	+
Sabatini et al., 2013 [12]	+	+	–	–	+	–	+
Sabatini et al., 2014 [14]	–	–	+	+	–	+	+
Sabatini et al., 2015 [16]	–	+	+	–	+	–	+
Tekçe et al., 2016 [20]	–	–	–	+	+	+	+
Verma et al., 2013 [13]	–	+	–	+	+	+	+

Fig. 3. Summary of risk of bias of included studies

Рис. 3. Сводка риска систематической ошибки во включенных исследованиях

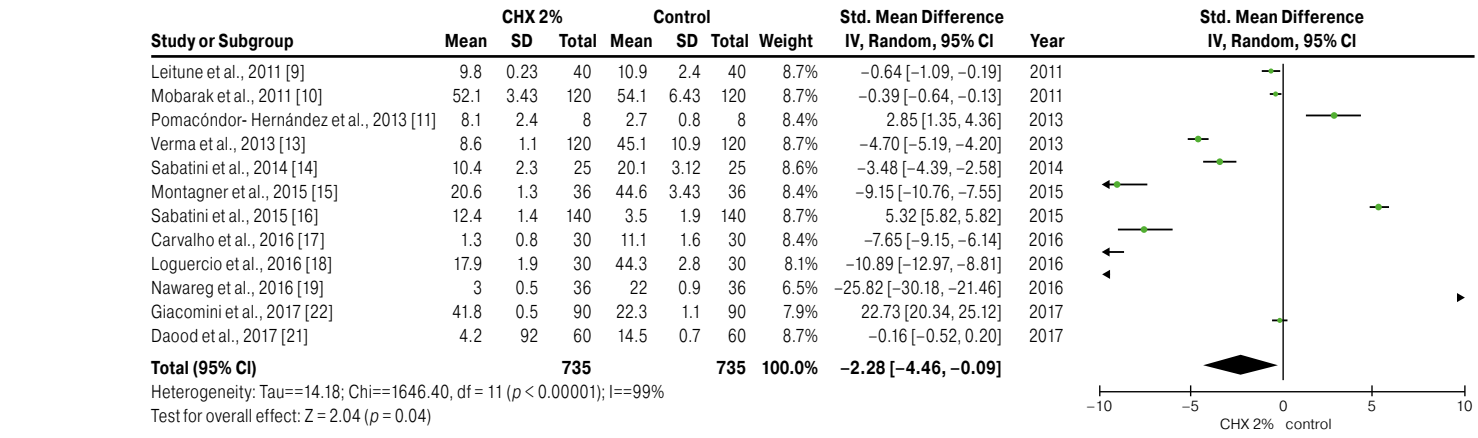

Fig. 4. Dentin bonding between 2% CHX and group

Рис. 4. Адгезия к дентину между 2% CHX и контрольной группой

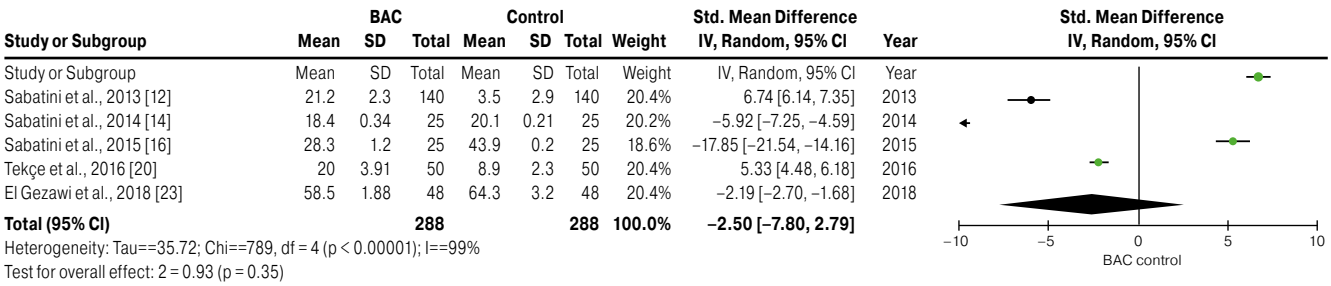

Fig. 5. dentin bonding between BAC and acid control group

Рис. 5. Адгезия к дентину между BAC и кислотной контрольной группой

As shown in Figure 5, the SMD is 2.50 (–7.80–2.79) and the pooled estimates favours BAC group signifying that overall greater dentin bonding on an average is 2.50 times greater in BAC group ($p > 0.05$).

DISCUSSION

Deeper demineralized zones are formed by hybrid layers created by bonding to Caries Affected Dentin (CAD) than to normal dentin. Often, the hybrid layer formed is thicker as compared to the normal dentin as CAD is more susceptible to acid etching due to partial demineralization. Hence, bonding is more difficult to CAD. Fully infiltrated demineralized dentin collagen produces an effective and long lasting structure [24]. Due to loss of intertubular dentin the ultimate tensile strength of CAD is found to be lesser then sound dentin. This can be attributed to the structural difference between CAD and sound dentin. CAD has been shown to have a lower mineral content which leads to a softer surface with high porosity [5]. The longevity of bonded restorations is compromised by MMPs, which are involved in both collagen degradation at the dentin–resin bonded interfaces and dentin matrix modification during caries progression. The effect of host-derived MMPs has been related to a reported reduction in bonding efficacy over time. The success of adhesive restoration can be enhanced by preventing the collagen degradation occurring due to the MMP's [25]. The action of MMPs on dentin results in modification of the structure and mechanical properties. Hence, MMP inhibitors come into play to inhibit this modification and pathological degradation. The use of MMP inhibitors not only halts the hybrid layer hydrolysis but also permits undisturbed remineralization and dentinal collagen breakdown during bonding with CAD [25].

Incorporation of MMP inhibitors into the hybrid layer has shown to improve the longevity of adhesive – resin interfaces. CHX, a potent cationic antimicrobial agent and a non-specific dentin MMP inhibitor, has shown positive results on being tested for its antiproteolytic effects. CHX molecule is large and water soluble and may leach out of the hybrid layer. This reduces its long-term antiproteolytic benefit [12]. Antimicrobial compounds containing positive charge bind to negatively charged phosphate and carboxylic groups in hydroxyapatite and collagen, respectively. Quaternary ammonium compounds (QACs) are cationic molecules with antimicrobial properties. Due to their smaller size as compared to CHX, it has been shown that they may display similar inhibitory effect on MMP's as well as allow easier stabilization [12]. BAC, a nitrogenous cationic surface-acting agent belonging to the quaternary ammonium group, has been used in dentistry as a cavity disinfectant, desensitizer, and endodontic irrigant [12].

Hardan et al. [26] in their systematic review and meta-analysis aimed to find complexities surrounding alternative techniques or strategies to fortify the bonding strength of commonly utilized adhesives in dentistry. Their search extended to databases up to 2020, where they curated a selection of in-vitro studies to form the backbone of their investigation. Screening through the entire data, they selected 74 studies for inclusion in their review, with an additional 61 studies earmarked for meta-analysis, each one offering a unique perspective on the multifaceted realm of dentin bonding. In their search, they found importance of the application of MMP inhibitors, the prolonged application times, the correct scrubbing techniques, the skill of selective dentin etching, the introduction of non-atmospheric plasma, intricacy of ethanol wet bonding, extended duration of blowing of bonding agent, the problem of multiple-layer applications, and the increased curing cycles – all contributing to the increase in dentin bonding strength. Their analysis indicated a significant statistical elevation in dentin bonding effectiveness with the judicious use of MMP inhibitors ($p < 0.01$).

In a similar way, Kiuru et al. [27] studied the impact of MMP inhibitors on overall dentin bonding. They selected 21 studies for meta-analysis and found that MMP inhibitors like 0.2–2% CHX showed promising results. Silva et al [28] revealed collagen cross-linking agents (CCLA) and their potential role in dentin biomodifications for enhanced adhesion. They selected three studies and found better outcomes with the use of CCLA. Lewis et al [29] studied the impact of MMP inhibitors on micro-tensile dentin bonding, bond durability, and mode of failure. Six studies were selected and they concluded that the application of MMP inhibitors improved bond durability and tensile bond strength, offering promise as a pre-treatment option in caries affected dentin.

In this review, 16 in-vitro studies fulfilled the eligibility criteria in which various dentin modifiers and MMP

inhibitors were included, of which 2% CHX (twelve studies [9–21]) and BAC (four studies [13; 15; 19; 22] being the most studied. The results of meta-analysis through pooled estimate of SMD suggested that 2% CHX 2.28 (–3.69–0.03) and BAC 2.50 (–7.80–2.79) had an overall greater dentin bonding compared to other control measures used.

CONCLUSION

Dentin bonding is crucial to the success and clinical longevity of restorations. Bond strength to CAD has been found to be lower than that of sound dentin. Dentin biomodifiers like BAC and MMP inhibitors like CHX when used on CAD have a positive influence on the bond strength of adhesives.

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