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Systematic Review

Optimizing Adhesive Bonding to Caries Affected Dentin: A Comprehensive Systematic Review and Meta-Analysis of Dental Adhesive Strategies following Chemo-Mechanical Caries Removal

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Abstract: Although there are several studies that have evaluated the bond strength of various adhesives to healthy dentin and caries-affected dentin after traditional caries removal, the objective of this systematic review aimed to assess the bond strength of various adhesives to caries-affected dentin (CAD) after chemo-mechanical caries removal (CMCR) treatment. The review adhered to PROSPERO protocol registration and followed PRISMA guidelines. The research question focused on the bonding effectiveness of dental adhesives to CAD after employing the chemo-mechanical caries removal method. PubMed, the TRIP database, and Scopus were searched, with the last search conducted in February 2023. Two reviewers independently screened and evaluated articles, resulting in 30 articles for full-text analysis out of 434 retrieved from databases. Twelve eligible studies were included in the review. The bond strength of etch-and-rinse (ER) and self-etch (SE) adhesive systems was assessed following CMCR treatment on CAD. SE adhesive systems exhibited higher bond strength to CAD compared to ER adhesive systems. Meta-analysis indicated that the bond strength achieved with self-etching adhesive systems remained consistent, regardless of the CMCR agent (Carisolv or Papacarie) used on dentin. The findings of this systematic review suggest that self-etch adhesive systems show favorable bond strength to caries-affected dentin following chemo-mechanical caries removal, regardless of the specific CMCR agent used. These results support the use of minimally invasive dentistry techniques aimed at preserving healthy tooth structure, dentin in particular.

Keywords: dentin; chemo-mechanical caries removal; dental adhesive; bond strength; caries-affected dentin; systematic review; meta-analysis; etch-and-rinse adhesive; self-etch adhesive

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1. Introduction

Dental caries remains a prevalent global disease, characterized by bacterial infection and mineral loss of hard dental tissues due to oral biofilm formation [1,2]. The major risk factors causing dental caries are enamel hypoplasia, eating habits, poor oral hygiene and trouble brushing, caregiver effect, low income, and low level of education [3–5]. Within carious dentin, two distinct layers play a critical role: the irreparable caries-infected dentin, also known as the outer layer, and the repairable caries-affected dentin (CAD), referred to as the inner layer [6]. Infected dentin exhibits significant decalcification, denatured collagen fibers, and disrupted odontoblasts, necessitating removal. In contrast, affected dentin displays minimal demineralization, relatively intact collagen fibers, and lacks bacterial invasion, requiring preservation [6–8].

Contemporary adhesive systems strive to achieve robust bonding to various tooth substrates, particularly to caries-affected dentin [9]. In the field of dentistry, there has been a paradigm shift towards minimally invasive and preventive approaches, transforming from G.V. Black's "extension for prevention" management to a "construction with conservation" mindset [10–12]. As a result, the search for less invasive yet effective caries excavation techniques has led to the development of minimally invasive methods that aim to remove only the infected dentin while preserving healthy enamel and dentin [13]. These techniques include air abrasion, sono-abrasion, and chemo-mechanical caries removal (CMCR) methods [12,14,15].

Chemo-mechanical caries removal (CMCR) is a non-aggressive approach involving the application of a chemical gel that selectively removes soft and necrotic infected dentin using a hand instrument while leaving the affected dentin intact [16]. CMCR agents can be categorized into sodium hypochlorite (NaOCl)-based (e.g., Caridex®, Carisolv®) and enzyme-based (e.g., Carie-Care™, Papacarie®, BRIX3000). Carisolv, a pink gel, contains sodium hypochlorite, amino acids (leucine, lysine, glutamic acid), methylcellulose, and erythrosine, acting by chlorinating and facilitating the removal of denatured collagen. On the other hand, Papacarie is an enzyme-based CMCR agent consisting of papain, a proteolytic enzyme with bactericidal and anti-inflammatory properties [17–21].

Bonding agents utilized in clinical practice can be classified into etch-and-rinse (ER), self-etch (SE), universal (U), and resin-modified glass ionomer adhesives (RMGIA) [22–24]. However, bonding to caries-affected dentin (CAD) poses challenges during operative treatment. The morphological alterations in CAD, including reduced mineral content, loss of crystallinity, and organic matrix changes, can impede dentin hybridization and compromise the mechanical performance of bonded restorations. High porosity and exposure of collagen fibers, along with a decrease in surface energy, are seen in the intertubular CAD. Reduction of these mechanical properties significantly influences a decrease of the mean elastic modulus and nano-hardness in CAD when compared to unaltered tissue. The obliteration of tubules can interfere with resin infiltration, at the same time preventing tags during bonding procedures. On the contrary, the lower mineral content of intertubular dentin in CAD permits deeper etching of this substrate [13–16].

Self-etch adhesives are the latest generation of adhesives. Adhesive frameworks today are either "etch and rinse" or "self-etch" approaches, which have different mechanisms of action on tooth substrate. Etch and rinse include pre-treatment with phosphoric acid etchant before bonding. Self-etch adhesives are acid-type monomers that perform etching and rinsing at the same time point [25,26]. They are easy to apply and have fewer clinical steps. Both systems structure mixed layers as resin infiltrates the permeable dentin and enamel [22,27]. However still, in clinical practice, etch and rinse system is used more than self-etch adhesives. Reduced bond strength of adhesive systems to CAD has been demonstrated, but little information is available about the bonding and comparison of these two adhesive systems to this clinically relevant substrate.

Therefore, this systematic review aims to evaluate the bond strength of dental adhesives to caries-affected dentin treated with chemo-mechanical caries removal agents, providing valuable insights into optimizing adhesive bonding strategies in caries management.

2. Materials and Methods

This systematic review's protocol was registered under PROSPERO registration number CRD42021283259. This non-Cochrane in vitro systematic review followed the four-phase flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [28]. The following PICO components were established, as presented in Table 1.

The following research question was developed: "What is the bonding effectiveness of different dental adhesives to caries-affected dentin after using chemo-mechanical caries removal method?"

Table 1. PICO components.

Population	Extracted human teeth with dental caries involving dentin removed with a chemo-mechanical removal agent
Intervention	Dental adhesives/Bonding agent (BA) application
Comparison	Etch-and-rinse, self-etch, and RMGIC adhesives
Primary Outcome	Assess the effect of CMCR agents on the bond strength of dental adhesives
Secondary Outcome	Analysis of failure mode of adhesives to CAD after using CMCR

2.1. Search Strategy

Following the PRISMA guidelines, a literature search (P.R.M. and L.M.) was conducted. Studies were identified through PubMed, the TRIP database, and Scopus. The authors established detailed search strategies for each database searched to identify studies for this review (Table 2).

Table 2. Search strategies.

Database	Keywords
PubMed	(((((“dental caries”[All Fields]) OR (“tooth cavity”[All Fields])) OR (“tooth cavities”[All Fields])) OR (“deep dental caries”[All Fields])) OR (“infected dentin”[All Fields])) OR (“affected dentin”[All Fields]) AND ((((((((((“chemomechanical caries removal”[All Fields]) OR (“atraumatic restorative treatment”[All Fields])) OR (“chemomechanical caries removal agents”[All Fields])) OR (“papacarie”[All Fields])) OR (“carie care”[All Fields])) OR (“brix3000”[All Fields])) OR (“carisolv”[All Fields])) OR (“caridex”[All Fields])) OR (“minimal invasive dentistry”[All Fields])) OR (minimal invasive caries excavation) OR (noninvasive dentistry) AND ((((“dental adhesives”[All Fields]) OR (“self-etch adhesives”[All Fields])) OR (“total etch adhesives”[All Fields])) OR (“resin-modified glass ionomer adhesive”[All Fields])) AND “bonding strength”[All Fields] OR (“bond strength”[All Fields]) OR (“adhesive strength”[All Fields]) OR (“binding strength”[All Fields]) OR (“cohesive strength”[All Fields]) OR (“binding force”[All Fields]) OR (“adhesive force”[All Fields])) OR (tooth bonding strength) OR (“microtensile bond strength”[All Fields]) OR (“microshear bond strength”[All Fields])
TRIP	Caries, caries removal, bonding agent, bond strength
Scopus	Caries AND chemomechanical AND caries AND removal AND instruments AND dental adhesive AND bond AND strength

The final search was performed in February 2023, with English language restrictions. References of each included study were also manually searched.

All the retrieved articles were introduced into a citation manager (EndNote v7.0, Clarivate Analytics, New York, NY, USA) to exclude duplicates.

2.2. Selection of Studies

All the studies were initially screened by titles by two reviewers (P.R.M. and L.M.), followed by the abstract evaluation when the title suggested potential inclusion. After the abstract was evaluated, eligible studies were selected for full-text reading. Complete texts of all the remaining publications were collected and reviewed, and only the articles that completely met the inclusion criteria were considered. In this selection, if there was a difference of opinion, a third reviewer (B.L.) was contacted to reach a consensus. Studies were identified based on eligibility criteria presented in Table 3.

Table 3. Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
In vitro studies	Review articles, case reports, anecdotes, letters to editors, clinical studies, observational studies
Studies performed in permanent human teeth only	Animal studies
Studies on dentin bond strength of dental adhesives to CAD after using CMCR agents	Studies on agents applied on dentin other than CMCR agents
Studies either comparing two or more CMCR agents or comparing different bonding agents using one CMCR agent.	Articles not relevant to the topic
Studies published after January 2000	Studies published before January 2000

2.3. Data Extraction

Based on the features of the studies and groups investigated, a standardized outline was utilized for data capture: author details, type of CMCR agent, procedure (caries removal method), sample size, type, name, and brand of adhesive systems, type of bond strength test used. Bond strength mean values and standard deviation were also extracted.

2.4. Assessment of Risk of Bias

The risk of bias (ROB) in the included studies was independently determined by two review authors (P.M. and L.M.). A modified CONSORT checklist of items for reporting in vitro studies of dental materials [29] was used to assess ROB. For each study, the following domains were considered: sample size calculation, samples with similar dimensions, control group, standardization of procedure, statistical analysis, and other risks of bias.

The risk was rated as low, medium, or high for each domain. One study was deemed to have a low risk of bias if the risk was low across the board. The study was classified as having a medium risk of bias if it had an unknown risk for at least two areas. The study was deemed to have a high risk of bias if it had a high risk in more than one domain.

2.5. Data Analysis

The studies' characteristics were listed in a descriptive summary. When enough information was available, a meta-analysis utilizing a random effects model was performed to determine the pooled mean differences between various dental adhesives after being subjected to Carisolv™ and Papacarie™ treatment. Bond strength data extracted were restricted to those from studies in which similar CMCR treatments were compared under the same conditions and when a pairwise comparison was available. All summary estimates were reported with mean with standard deviation and corresponding 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the Cochrane Q statistic and I2 test (>75% indicates high heterogeneity). The analyses were conducted using Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

The electronic search identified 434 articles from PubMed, the TRIP database, and Scopus. After the removal of duplicated articles, the total number of articles was found to be 333. However, after screening articles based on abstracts and titles, a total of 30 articles could be assessed. Finally, the total number of full-text articles found to be eligible for the study was 12 (Figure 1).

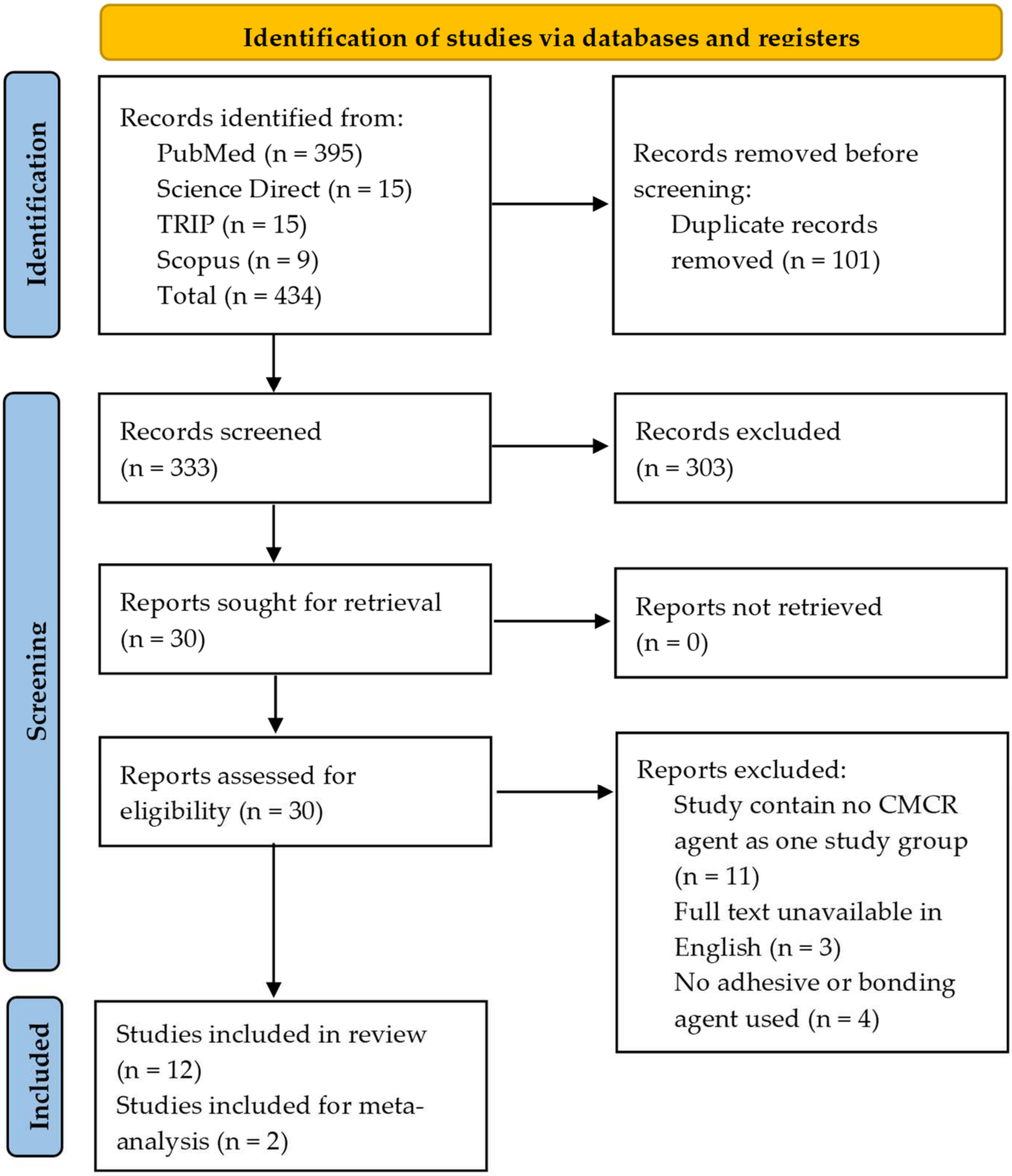

Figure 1. PRISMA flow diagram of literature search.

3.1. Characteristics of Included Studies

Eleven studies [6,9,30–38] used Carisolv as the CMCR agent (Table 4). Another CMCR agent used in four studies [31–33,39] was Papacarie. All bonding agents used in the included studies were presented in Table 5.

Table 4. CMCR agents used in the included studies.

CMCR Agent	Composition	Article
Carisolv™	0.95% sodium hypochlorite, three amino acids (glutamic acid, leucine, lysine), pH = 11	Kusumasari et al., 2021 [31] Hamama et al., 2015 [32] Hamama et al., 2014 [33] Aggarwal et al., 2013 [34] Sirin Karaarslan et al., 2012 [35] Li et al., 2011 [30] Neves et al., 2011 [38] Banerjee et al., 2010 [36] Sonoda et al., 2005 [6] Burrow et al., 2003 [9] Haak et al., 2000 [37]
Papacarie™	Papain enzyme, chloramine, toluidine blue, salts, preservatives, thickeners, stabilizers, and deionized water. (pH = 9.2)	Kusumasari et al., 2021 [31] Hamama et al., 2015 [32] Hamama et al., 2014 [33] Piva et al., 2008 [39]
SFC-V ("Biosolv")	pepsin, phosphoric acid/sodium biphosphate buffer	Banerjee et al., 2010 [36]
SFC-VIII	a moderately acidic buffered solution of pepsin	Neves et al., 2011 [38]

The characteristics of the included studies are summarized in Tables 6 and 7. Eleven studies [6,9,13,30–36,39] used the microtensile bond strength test (μTBS), whereas one study [37] used the shear bond strength (SBS) test. Evaluation of μTBS was performed using the universal testing machine at a crosshead speed of 1 mm/min [9,30–33,35,36,38,39].

On fracture mode analysis (Table 8) in the self-etch adhesives group, four studies [9,32,33,38] showed cohesive failure in resin composites or within caries-affected dentin, whereas six studies [6,30,35–37,39] showed adhesive failure between bonding resin and caries affected dentin. One study [31] showed mixed, partially adhesive, and partially cohesive failure within caries-affected dentin. Meanwhile, in etch-and-rinse adhesives, four studies [30,35,37,39] predominantly showed adhesive failure, and two studies [6,36] showed cohesive failure mode.

Table 5. Dental adhesives used in the included studies.

Type of DA	Steps in Application of DA	DA System	Composition of DA	Manufacturer Instructions for Application	Author
ER	3-step	Single Bond (3M ESPE, St Paul, MN, USA)	Dimethacrylates, HEMA, polyalkenoid acidcopolymer, 5 nm silane treated colloidal silica, ethanol, water, photoinitiator.	1. Apply etchant, wait for 15 s, and rinse for 10 s. 2. Blot excess water. 3. Apply 2 coats of adhesive for 15 s. 4. Gently air thin for 5 s. 5. Light-cure for 10 s.	Aggarwal et al., 2013 [34]
		Adper Scotchbond 1XT (3M ESPE, Germany)	2 hydroxy ethylmethacrylate (HEMA), Polyalkenoic acid copolymer, Bis-phenol A diglycidylmethacrylate (Bis-GMA), Water camphorquinone, Ethanol	1. Apply etchant, wait for 15 s, and rinse for 10 s. 2. Remove excess water with air or blotting 3. Apply primer and dry for 5 s 4. Apply BA and light cure for 10 s	Banerjee et al., 2010 [36]
	2-step	Adper Single Bond 2 (3M ESPE, Germany)	Bis-GMA, HEMA, dimethacrylates, ethanol, water, photoinitiator, methacrylate, functional copolymer of polyacrylic and poly(itaconic) acids, 10 wt% of 5 nm-diameter spherical silica particles (pH = 4.1)	1. Rinse and blow dry excessive water 2. Adhesive application 3. Gentle air stream 4. Light polymerize 10 s	Sirin Karaarslan et al., 2012 [35]
		One-Step (Renew Bisco, Schaumburg, IL, USA)	BPDMA, HEMA, acetone (pH = 4.1)	1. Rinse for 30 s and dry for 15 s 2. Dentin rewetted with 3.5 mL water 3. Two coats of adhesive for 10 s each 4. Air dry for 10 s 5. Light cure for 10 s	Li et al., 2011 [30]
		Prime and Bond NT (Dentsply)	PENTA, UDMA, nanofiller, cethylamine hydrofluoride, acetone	1. Rinse and blot dry 2. Adhesive application 3. Gentle air stream 4. Light polymerize 10 s	Li et al., 2011 [30]; Piva et al., 2008 [39]; Sonoda et al., 2005 [6]; Haak et al., 2000 [37]

Table 5. *Cont.*

Type of DA	Steps in Application of DA	DA System	Composition of DA	Manufacturer Instructions for Application	Author
Mild SE (pH ≥ 2)	2-step	One Coat Self-Etching Bond, (Coltene Whaledent, Altstatten, Switzerland) pH = 2.5	Primer: water, HEMA, acrylamidosulfonic acid, glycerol mono- and dimethacrylate, methacrylized polyalkenoate. Bonding: HEMA, glycerol mono- and dimethacrylate, UDMA, methacrylized polyalkenoate, camphoroquinone.	1. Apply primer with gentle agitation for 20 s. 2. Gently air thin for 2 s. 3. Apply bonding agent with gentle agitation for 20 s. 4. Gently air thin for 2 s. 5. Light-cure for 10 s.	Aggarwal et al., 2013 [34]; Burrow et al., 2003 [9]
		Clearfil SE Bond (Kuraray Co, Osaka, Japan) pH = 2	Dimethacrylate, dl-camphorquinone, N,N-diethanol-p-toluidine, water; Adhesive Resin: MDP, Bis-GMA, HEMA, hydrophobic dimethacrylate, dl-camphorquinone, N,N-diethanol-p toluidine, silanated colloidal silica		Kusumasari et al., 2021 [31]; Hamama et al., 2014 [33]; Sirin Karaarslan et al., 2012 [35]; Neves et al., 2011 [38]; Piva et al., 2008 [39]; Burrow et al., 2003 [9]
		Clearfil Protect Bond (Kuraray Medical Inc, Tokyo, Japan) pH = 4.5	MDP, HEMA, Hydrophilic dimethacrylate, Water, Bis-GMA, Hydrophobic dimethacrylate, DL-Camphorquinone, N,N-Diethanol-p-toluidine		Sonoda et al., 2005 [6]
Intermediate SE		Syntac SC (Vivadent, Schann, Liechtenstein) pH = 1.6	2 HEMA, methacrylic acid modified polyacrylic acid, maleic acid, water, fluoride	1. Application of Syntac SC, 20 s. 2. Solvent removal by air blowing, 5 s. 3. Light-cure, 20 s. 4. Application of Syntac SC. 5. Immediate solvent removal by air blowing, 5 s. 6. Light-cure, 20 s.	Haak et al., 2000 [37]
		Filtek Silorane adhesive pH = 2.7	3 Silorane (3,4-epoxycyclohexylethylcyclo polymethylsiloxane, bis-3,4-epoxycyclohexylethyl-phenylmethylsilane); Fillers: Quartz (silane layer), radiopaque yttrium fluoride filler	1. Application of primer 10 s 2. Gently air dry 3. Light cure 10 s 4. Apply BA 5. Air dry 6. Light cure for 10 s	Banerjee et al., 2010 [36]

Table 5. *Cont.*

Type of DA	Steps in Application of DA	DA System	Composition of DA	Manufacturer Instructions for Application	Author
Mild SE	1-step	Adper Easy Bond Self-Etch Adhesive (3M ESPE, St Paul, MN, USA) pH = 2.3	Methacrylated phosphoric esters, dimethacrylates, 2-HEMA, polyalkenoid acid copolymer, colloidal silica, ethanol, water, photoinitiator.	1. Apply bonding agent with gentle agitation for 20 s. 2. Dry for 5 s. 3. Light-cure for 10 s.	Aggarwal et al., 2013 [34]
		Clearfil Universal Bond Quick ER (Kuraray Noritake Dental Inc., Tokyo, Japan) pH = 2.3	10-MDP, Bis-GMA, HEMA, hydrophilic amide monomer, colloidal silica, ethanol, dl-CQ, accelerators, water, sodium fluoride. (pH = 2.5) Primer: 10-MDP, 2-HEMA, hydrophilic aliphatic dimethacrylate, dl-CQ, water	1. Apply and leave for 10 s 2. Dry with air jet for 5 s 3. Light cure for 10 s	Kusumasari et al., 2021 [31]
		Clearfil S3 (Kuraray Medical Inc, Tokyo, Japan) pH = 2.7	10-MDP, bis-GMA, HEMA, di-camphorquinone, ethanol, water, silanated colloidal silica		Hamama et al., 2014 [33]
Intermediate SE (pH = 1.5)		G-Bond (GC Corporation Tokyo, Japan) pH = 1.5	4-MET, UDMA, dimethacrylate component, phosphoric ester monomer, acetone, water		Sirin Karaarslan et al., 2012 [35]
Strong SE (pH ≤ 1)		Etch&Prime 3.0 (Degussa AG) pH = 0.76	HEMA, pyrophosphate monomer, photoinitiators, ethanol, water		Haak et al., 2000 [37]
		Adper Prompt-L-Pop (AD-3M ESPE, St. Paul, MN, USA) pH = 0.8	Methacrylated phosphoric acid HEMA-esters, Bis-GMA, initiators based on camphorquinone, and stabilizers		Banerjee et al., 2010 [36]

Table 5. *Cont.*

Type of DA	Steps in Application of DA	DA System	Composition of DA	Manufacturer Instructions for Application	Author
RMGIA	Self-adhesive material	Fuji II LC (GC International)	Fluoroaluminium silicate glass, polyacrylic acid, HEMA	1. Apply GC Cavity Conditioner to remove the smear layer and seal the dentin tubules. 2. Place the mixed Fuji II LC into the cavity. 3. Light cure, trim, and finish.	Burrow et al., 2003 [9]
		Fuji Bond LC (GC Corp, Tokyo, Japan)	Powder: 90–100%, Alumino-fluoro-silicate glass (amorphous); Liquid: 20–30% distilled water, 20–30% PAA, 25–35% HEMA, 5–10% UDMA, and less than 1% Camphorquinone		Hamama et al., 2015 [32]
		Riva Bond LC (SDI, Bayswater, Australia)	Compartment 1: 95–100% Fluoroaluminosilicate glass powder; Compartment 2: 15–25% PAA, 1–5% Tartaric Acid 25–40% HEMA, 5–15% Dimethacrylate Cross-linker 10–20% Acidic Monomer	1. 25–30% PAA (Riva conditioner) for 10 s 2. excavated surfaces were bonded and then incrementally covered (2-mm thick increments) Riva LC RMGIC restorative materials cured for 20 s using a light-emitting diode	Hamama et al., 2015 [32]

SE = self-etch; ER = etch-and-rinse; DA = dental adhesive; PAA = polyacrylic acid; RMGIA = resin-modified glass ionomer adhesive; HEMA, 2-Hydroxyethyl methacrylate; Bis-GMA, adduct of bisphenol A and glycidyl methacrylate; UDMA, urethane dimethacrylate;PENTA, dipentaerythritol pentaacrylate monophosphate; RMGIC = resin-modified glass ionomer cement.

Table 6. Characteristics of the included study for qualitative analysis.

Author	CMCR Agent	Time of Exposure	Sample Type	Sample Size	Storage Conditions	Bond Strength Test Used	Tensile Rate
Kusumasari et al., 2021 [31]	Carisolv and Papacarie	60 s	Extracted human molars with occlusal carious lesions	40	24 h water storage	μTBS	1 mm/min
Hamama et al., 2015 [32]	Carisolv and Papacarie	30 s	Permanent molars exhibiting moderate cavitation on the occlusal surface into dentine	75	distilled water at 37 °C for 24 h	μTBS	1 mm/min
Hamama et al., 2014 [33]	Carisolv and Papacarie	30 s	Carious permanent molars exhibiting frank cavitation into dentin	48	distilled water at 37 °C for 24 h	μTBS	1 mm/min
Aggarwal et al., 2013 [34]	Carisolv	30 s	Extracted, non-restored human maxillary and mandibular third molars with occlusal dental caries	30	distilled water at 37 °C for 24 h	μTBS	0.5 mm/min
Sirin Karaarslan et al., 2012 [35]	Carisolv	30 s	Permanent cavitated human molar teeth	45	immersion in water at 37 °C for 24 h	μTBS	1 mm/min
Li et al., 2011 [30]	Carisolv	30 s	Extracted human third molars with moderate occlusal caries	45	distilled water at 37 °C for 24 h	μTBS	1 mm/min
Sonoda et al., 2005 [6]	Carisolv	30 s	Extracted adult human molars	20	One day stored in tap water at room temperature	μTBS	0.2 mm/min
Burrow et al., 2003 [9]	Carisolv	30 s	Freshly extracted human molars with occlusal caries	31	water at 37 °C for 24 h	μTBS	1 mm/min
Neves et al., 2011 [38]	Carisolv; Exp. SFC-VIII + instrument	30 s	Non-restored molar presenting caries lesions on the occlusal surface that presumably involve dentin	35	24-h storage in water at 36 °C,	μTBS	1 mm/min
Banerjee et al., 2010 [36]	Carisolv; SFC-V ("Biosolv")	40 s; SFC-V was introduced into the cavity and was immediately agitated.	Extracted, human cavitated carious molars	51	hydrated four-week storage	μTBS	1 mm/min
Piva et al., 2008 [39]	Papacarie	30 s	Cavitated human molar teeth	40	37 °C in distilled water for 24 h	μTBS	1 mm/min
Haak et al., 2000 [37]	Carisolv	30 s	Extracted human molars with occlusal caries	121	immersed in water at 37 °C for 24 h	SBS	1 mm/min

CMCR = chemo-mechanical caries removal; μTBS = microtensile bond strength; SBS = shear bond strength.

Table 7. Characteristics of the study for quantitative analysis.

Author	CMCR Agent	Bonding Agent	Bond Strength to CAD (Mean ± SD) [MPa]	Conclusion
Aggarwal et al. 2013 [34]	Carisolv	Single-Bond (ER)	31.1 ± 2.7	Carisolv did not affect the µTBS values of different adhesive systems tested on CAD. The ER adhesive and two-bottle SE system showed significantly µTBS than the single-bottle SE system.
		Adper Easy Bond (SE)	23.4 ± 2.2	
		One Coat (SE)	33.1 ± 3.8	
Sirin Karaarslan et al., 2012 [35]		Adper Single Bond 2 (ER)	11.7 ± 5	The technique used to remove caries influenced the µTBS to CAD created by the dentin adhesive systems. CMCR techniques may be suggested when choosing a two-step SE adhesive.
		Clearfil SE Bond (SE)	19 ± 5.4	
		G-Bond (SE)	14.4 ± 3.7	
Li et al., 2011 [30]		Prime and Bond NT (ER)	17.22 ± 7.95	CMCR did not influence the bond strengths of the adhesive systems used in this study to CAD. The highest bond strength was achieved with the application of the ER adhesive system.
		ONE-STEP (ER)	25.4 ± 8.44	
		Adper Prompt L-Pop (SE)	17.96 ± 8.33	
Banerjee et al., 2010 [36]		Scotchbond (ER)	126.11 ± 37.53	Using three different caries excavation techniques (Carisolv ™ gel, SFC-V, and hand excavation) has no effect on adhesive bond strengths to residual carious dentin.
		Filtek Silorane Bond (ER)	134.49 ± 38.43	
Sonoda et al., 2005 [6]		Clearfil Protect Bond (SE)	31.10 ± 9.21	Carisolv gel excavation did not compromise bond strengths to CAD in either group tested.
		Prime and Bond NT (ER)	26.99 ± 11.69	
Burrow et al., 2003 [9]		Clearfil SE Bond (SE)	28.7 ± 6.9	Carious dentin treated with Carisolv did not affect the adhesion of the adhesive restorative materials tested in this study, except Fuji II LC.
		One Coat Bond (ER)	27.4 ± 6.4	
		Fuji II LC	16.4 ± 5.6	
		Fuji IX	13.4 ± 3.9	
Haak et al., 2000 [37]		NRC/Prime and Bond NT (ER)	13.4 ± 3.2	CMCR has no negative impact on bonding modern adhesive systems to dentin.
		Prime and Bond NT (ER)	20.8 ± 5.1	
		Syntac SC (SE)	21.4 ± 5.4	
		PPA/Syntac SC (SE)	18.6 ± 4.6	
		Etch and Prime 3.0 (SE)	17.3 ± 3.3	
Kusumasari et al., 2021 [31]		Clearfil SE Bond 2 (SE)	47.35 ± 5.7	Smear layer deproteinization using CMCR agents (Papacarie and Carisolv) is an effective pre-treatment to improve the µTBS of two-step SE adhesives, particularly to CAD.
		Universal Bond Quick ER (SE)	42.25 ± 8.3	
Hamama et al., 2015 [32]		PA/Fuji Bond LC (RMGIC adhesive)	22.58 ± 4.25	Tested CMCR agents have no adverse effect on the adhesion of RMGIA to both sound dentin and CAD. Dentin surface treatment with 37% phosphoric acid for 5 s has no detrimental effects on the bonding of RMGI adhesives to dentin when compared with either PAA solution for 10 s. RMGIA bonded well to both sound dentin and CAD.
		25–30%PAA/Fuji Bond LC	15.4 ± 1.69	
		25–30% PAA/Riva Bond LC	14.5 ± 5	
		20% PAA + 3% AlCl3/Fuji Bond LC	20.4 ± 2.2	
		PA/Riva Bond LC	15.3 ± 1.9	

Table 7. *Cont.*

Author	CMCR Agent	Bonding Agent	Bond Strength to CAD (Mean ± SD) [MPa]	Conclusion
Hamama et al., 2014 [33]	Carisolv	Clearfil SE Bond (SE)	30.8 ± 2.7	CMCR did not affect the bonding of SE adhesives to CAD.
		Clearfil S3 Bond (SE)	20.1 ± 2.2	
Neves et al., 2011 [38]		Clearfil SE Bond	41.7 ± 11.7	Carisolv resulted in the highest TBS to "residual caries-excavated" dentin, followed by the use of a tungsten-carbide-bur in conjunction with Caries Detector.
	SFC-VIII		46 ± 11.5	
Piva et al., 2008 [39]	Papacarie	Clearfil SE Bond (SE)	10.9 ± 2.3	The bond strength of the SE adhesive to CAD was negatively affected by chemo-mechanical excavation using the papain-based gel.
		Prime and Bond NT (ER)	8.3 ± 8.3	
Kusumasari et al., 2021 [31]		Clearfil SE Bond 2 (SE)	46.56 ± 3.5	
		Universal Bond Quick ER (SE)	45.19 ± 5.9	
Hamama et al., 2015 [32]		PA/Fuji Bond LC (RMGIC adhesive)	21.44 ± 4.94	
		25–30% PAA/Fuji Bond LC	15.9 ± 1.66	
		25–30% PAA/Riva Bond LC	15.5 ± 3.9	
		20% PAA + 3% AlCl3/Fuji Bond LC	16.1 ± 3.1	
		PA/Riva Bond LC	18.2 ± 3.1	
Hamama et al., 2014 [33]		Clearfil SE Bond (SE)	31.5 ± 2.8	
		Clearfil S3 Bond (SE)	23.2 ± 1.9	
Banerjee et al., 2010 [36]	SFC-V (Biosolv)	Scotchbond (ER)	264.71 ± 79.3	Utilizing three distinct caries extraction methods (Carisolv ™ gel, SFC-V, and hand excavation) has no effect on adhesive bond strengths to residual carious dentin.

CMCR = chemo-mechanical caries removal; CAD = caries-affected dentin; SE = self-etch; ER = etch-and-rinse; RMGIA = resin-modified glass ionomer adhesive.

Table 8. Type of failure mode of bonding agents after CMCR application is reported in the included studies.

Author	Type of Failure Mode of Bonding Agents after CMCR Application	
	Self-Etch Adhesives	Etch-and-Rinse Adhesives
Hamama et al. (2015) [32]	Cohesive	Na
Hamama et al. (2014) [33]	Cohesive	Na
Neves et al. (2011) [38]	Cohesive	Na
Banerjee et al. (2010) [36]	Adhesive	Cohesive
Sonoda et al. (2005) [6]	Adhesive	Cohesive
Burrow et al. (2003) [9]	Cohesive	Na
Sirin Karaarslan et al. (2012) [35]	Adhesive	Adhesive
Li et al. (2011) [30]	Adhesive	Adhesive
Piva et al. (2008) [39]	Adhesive	Adhesive
Haak et al. (2000) [37]	Adhesive	Adhesive
Kusumasari et al. (2021) [31]	Mixed	Na

3.2. Quality Assessment of Included Studies

Figure 2 presents the findings of the risk of bias analysis and Figure 3. Four studies [6,31,38,39] were classified as low risk, seven studies [9,30,32–36] were classified as medium risk, and only one study [37] was classified as high risk of bias.

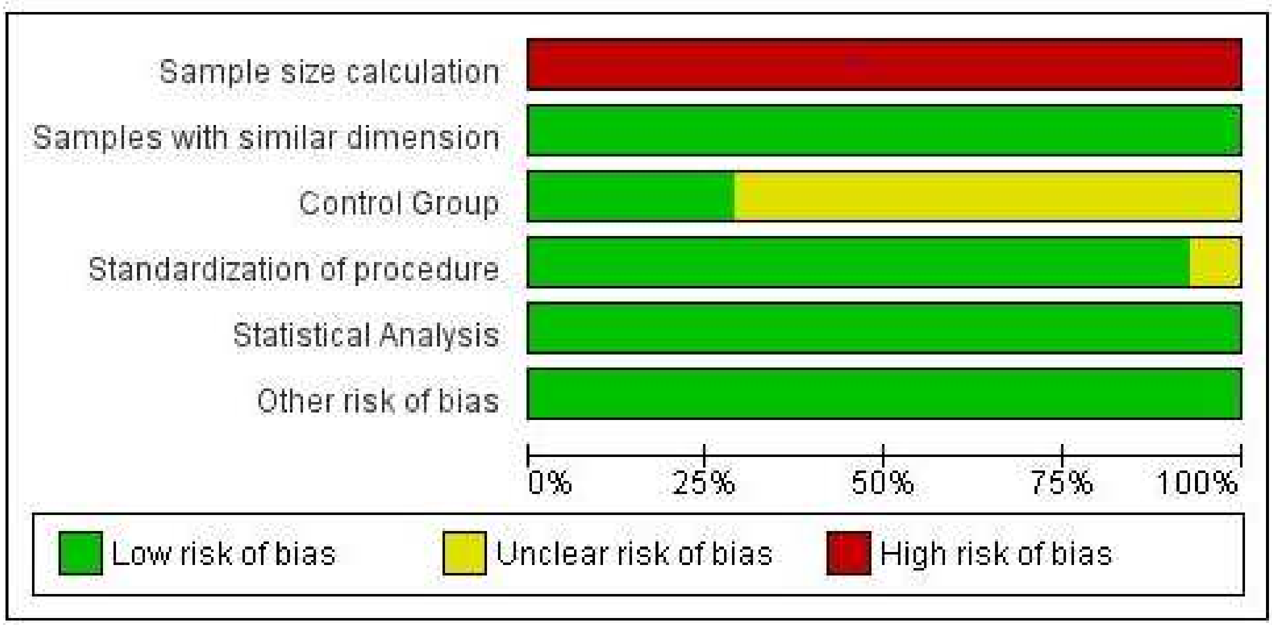

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item, presented as percentages across all included studies.

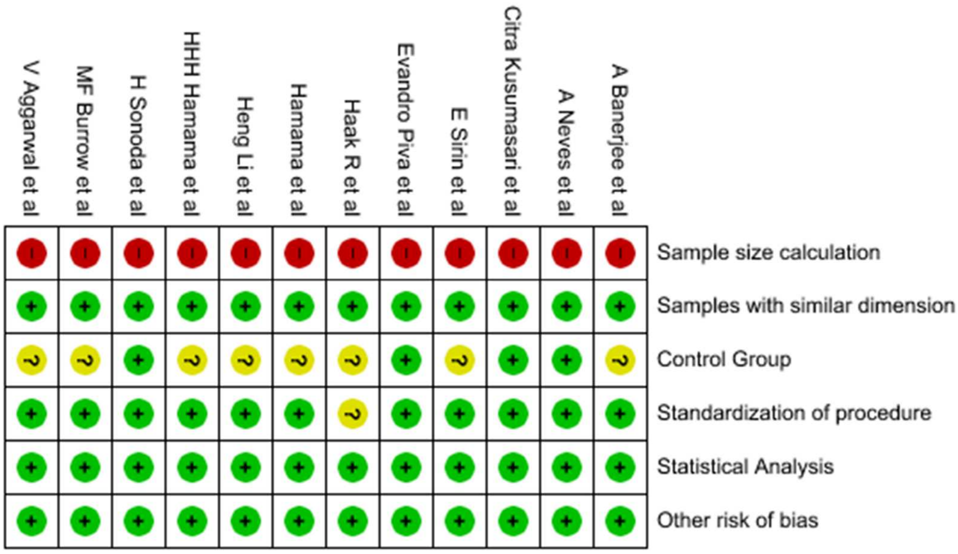

Figure 3. Summary of risk of bias: evaluations of each study's included item's risk of bias [6,9,30–39].

It was found that none of the studies mentioned sample size calculation. One study [37] did not mention the standardization of the procedure, and seven studies [9,30,32–37] did not clearly mention the control group in their respective studies.

3.3. Meta-Analysis

The meta-analysis (Figure 4) included only two studies [31,33] that compared the bond strength of self-etch adhesive (Clearfil SE bond) to caries-affected dentin after it was subjected to Carisolv™ and Papacarie™ treatment. The meta-analysis depicted that SE adhesive allowed to achieve similar bond strength to CAD whether it was treated with Carisolv or Papacarie.

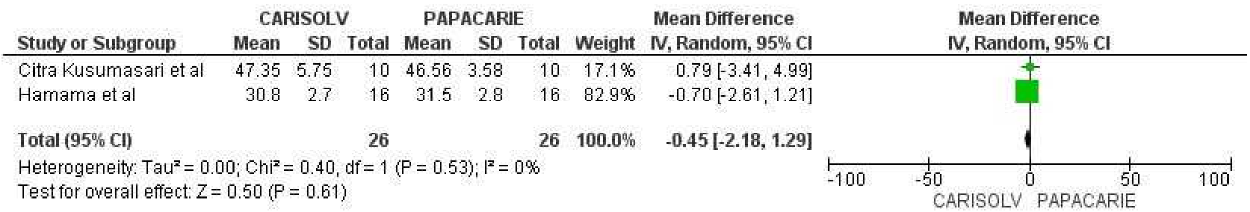

Figure 4. Meta-analysis comparing the dentin bond strength of Clearfil SE Bond (SE adhesive) in caries-affected dentin after Papacarie and Carisolv application [31,33].

4. Discussion

Compared to enamel, dentin has always posed a challenge for bonding [40–42], likely due to its more heterogeneous structure. Dentin is a composite material consisting of approximately 50 vol% mineral phase, 30 vol% collagen, and 20 vol% water [43]. Therefore, the bonding strategy for dentin focuses on two phases: the mineral phase, mainly composed of carbonate-rich hydroxyapatite, and the organic phase, primarily collagen, in a moist environment.

The bonding method for dentin was evaluated in the current investigation. Since it is the most typical substrate in clinical practice, the bonding to carious dentin was assessed. Changes caused by carious lesions result in poorer dentin hybridization [44,45]. In the present study, the bond strength to caries-affected dentin was lower due to low mineral content, which affected dentin hybridization.

Carious dentin is composed of two distinct layers: an outer layer of infected dentin and an inner layer of affected dentin [46]. Fourier-transform infrared imaging (FTIR) analysis of caries-affected dentin (CAD) has revealed lower mineral content and reduced crystallinity in the mineral phase compared to normal dentin. The loss of mineral from the dentin matrix during the carious process is replaced by water, which can account for up to 53% of the volume in CAD [47]. In addition, most clinical substrates are covered with smear layers, which hinder the penetration of adhesive molecules into tooth substances [44,48]. The occlusion of tubules in CAD leads to decreased permeability. Following cavity preparation and removal of CAD, the cavity floor is largely made up of dentin that has been damaged by caries, making it the most common bonding substrate, as opposed to sound dentin. CAD differs from sound dentin in terms of hardness, being twice as soft, even though mineral depositions occlude dentinal tubules. The mineral deposits in CAD, such as plate-like β-octocalcium phosphate (whitlockite), are not as densely packed and are therefore softer than well-packed apatite, although they may be more acid-resistant [49]. Moreover, the ultimate tensile strength of CAD is lower than that of sound dentin, possibly due to the loss of mineral in intertubular dentin. The matrix of demineralized CAD, according to a study, was just as durable as that of healthy dentin. The partial demineralization in CAD may reduce the number of MDP-dentin bonding sites and affect the chemical bonding of adhesives to CAD [50]. The lower bond strength in caries-affected dentin can be attributed to the lower mineral content surrounding and within collagen fibrils, resulting in a softer surface with a higher degree of porosity compared to sound dentin [51].

In this systematic review, which included 12 studies, the bond strength of different adhesives (etch-and-rinse, self-etch, and resin-modified glass ionomer adhesive) on CAD after treatment with chemo-mechanical caries removal (CMCR) agents was assessed. Eleven studies used Carisolv, while four studies used Papacarie. One study used SFC-V (Biosolv), and another used SFC-VIII as CMCR agents compared to Carisolv.

CMCR agent Carisolv has a proteolytic action, using a combination of enzymes to selectively degrade the collagen matrix of carious dentin. The enzymes in Carisolv, such as collagenase and papain, break down the denatured collagen fibrils present in carious dentin, facilitating its removal [52]. This enzymatic action is believed to be less aggressive towards sound dentin compared to mechanical methods, as it selectively targets the demineralized and degraded collagen structure [53–55]. The CMCR method did not have any adverse effects on the bonding of adhesives to CAD [6,9,16,30,32–34,36,37]. Caries removal with either NaOCl-based or enzyme-based CMCR methods resulted in the partial (Carisolv) or complete (Papacarie) absence of the smear layer and irregular surface characteristics when observed under SEM at 2000× magnification [31,56]. These surface characteristics may affect resin infiltration into the dentin and enhance micromechanical adhesion, leading to good resin infiltration in caries-affected dentin groups [57]. Pre-treatment of dentin with NaOCl derivatives, particularly in caries-affected regions, was found to promote the adhesion of self-etch adhesives to CAD [58]. The predominance of adhesive failures when bonding to carious dentin is likely related to the difficulty of the adhesive to completely infiltrate the exposed and altered collagen mesh [39]. The demineralization and remineralization processes that occur during caries result in the occlusion of dentinal tubules with larger, less soluble calcium phosphate crystals, further affecting adhesion. Additionally, the organic matrix of carious dentin differs from that of the normal substrate due to denatured collagen fibrils, which can also influence the fracture mode [39].

Various techniques are available to evaluate bond strength, with the most commonly used being tension or shear modes [59–62]. In this systematic review, 13 studies assessed microtensile bond strength (μTBS), while one study evaluated shear bond strength. Tensile bond strength tests require special testing jigs and meticulous procedures [8,62]. Shear bond strength tests, although easier to perform, generate non-uniform stress concentration at the edge of the bonded interface during testing [63,64].

To overcome the limitations of conventional shear or tensile bond strength tests, the μTBS test was introduced. It involves bonding adhesive resins to the entire flat occlusal surface of teeth, which is then covered with a resin composite. Subsequently, the specimen is vertically sectioned into multiple serial sections, creating an hourglass shape for maximum stress development at that region [65,66]. The μTBS test, along with morphological and spectroscopic investigations, has contributed to improving resin/dentin adhesion and has shown greater discriminative power than traditional macro-shear tests [67]. This test is considered a versatile and standard method for bond strength testing, providing better control of regional differences and making more economical use of teeth. Moreover, it allows the exclusive evaluation of adhesive bond failures when the bonded surface area is approximately 1 mm^2, leading to better stress distribution at the true interface [66,68,69].

Regarding the failure mode of restorations, they can fail within the restoration itself, at the restoration and bonding adhesive interface, at the restoration and substrate interface, or only at the substrate. Cohesive failure occurs within the resin composite or dentin, adhesive failure refers to failure between dentin and bonding resin, and mixed failure involves a combination of adhesive and cohesive failures.

When bonding to caries-affected dentin, an analysis of failure modes of dental adhesives showed an increased incidence of cohesive failures, possibly due to differences in the nature of the bond. The thickness of the hybrid layer or increased dentin moisture after Carisolv treatment may contribute to a slightly higher number of microscopic defects in the bonded layer as a whole. Additionally, the slight difference in dentin hardness after using Carisolv or other differences in the dentin itself can influence the failure mode [9,16,37,39].

It is essential to keep in mind that the findings of this systematic review indicated that both Carisolv and Papacarie were equally effective in dentinal caries removal and showed similar bond strength to adhesive systems [49,50,70]. However, one group of investigators reported marginally better clinical parameters for Papacarie, particularly about the length of the treatment and the number of dental cavities encountered [49,50,70]. The mode of action of Papacarie involves breaking partially degraded collagen molecules, contributing to the degradation and elimination of the fibrin "mantle" formed during the carious process. Papacarie's papain enzyme specifically targets dead cells and infected tissues lacking or showing no antitrypsin, which inhibits protein digestion. Therefore, sound collagen fibers in the inner affected and normal dentin are not affected by Papacarie [71].

Despite the promising results of Carisolv and Papacarie in terms of bond strength and clinical parameters, it is important to consider that the success of adhesive restorations depends on various factors beyond caries removal alone. Factors such as proper isolation, effective moisture control, adhesive system properties, and technique sensitivity can significantly influence the longevity and durability of the restoration.

Furthermore, it is worth mentioning that the studies included in this systematic review had certain limitations, including variations in methodology, small sample sizes, and heterogeneity in the adhesive systems and protocols used. In the included articles, no standardized protocols were followed, brief details about the control groups were not mentioned, and the method of randomization into groups was not mentioned in any of the articles. These factors can introduce bias and affect the generalizability of the findings. Therefore, further well-designed studies with standardized protocols are needed to provide more robust evidence on the influence of Carisolv and Papacarie on bond strength to caries-affected dentin.

In conclusion, the selection of a caries removal method can impact the bond strength of adhesive restorations to carious dentin. Carisolv and Papacarie have shown comparable bond strength to adhesive systems when used for caries removal. Their selective removal of carious tissue while preserving sound dentin provides a potentially favorable substrate for bonding. However, it is essential to consider various factors and ensure proper technique and protocol adherence to achieve optimal bonding outcomes.

The present systematic review has some limitations as articles included in the review had low sample sizes, heterogeneity in the adhesive systems, and no proper information about the control group in the studies was provided. In addition, no standardized protocols were mentioned and followed. It is important to note that the quality of the studies included in the systematic review varied, indicating a need for further high-quality research.

Additional research is necessary to confirm the findings of this review and identify optimal strategies for chemo-mechanical caries removal and bonding techniques in order to enhance clinical outcomes. Further research is needed to elucidate the long-term clinical performance and stability of adhesive restorations using these caries removal methods.

Further research on biomimetic dental adhesives and dental restorative materials containing bioactive particles should be conducted as they may exhibit remineralizing potential to enamel and/or dentin-resin interface [72–75].

5. Conclusions

As a result of the systematic review conducted, the findings that follow can be drawn.

1. The use of chemo-mechanical caries removal agents did not significantly affect the bond strength of dental adhesives to caries-affected dentin;
2. Two-step self-etch adhesives exhibited higher bond strength compared to etch-and-rinse adhesives when applied on caries-affected dentin. Unlike ER, which destroys collagen fibrils, SE preserves the collagen fibrils and hence superior performance;
3. Both Carisolv and Papacarie showed corresponding bond strength to dentin when utilized in conjunction with self-etch dental adhesives.

Hence, chemo-mechanical caries removal agents should be used routinely for caries removal as it is a conservative method and also patient friendly.

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