EVALUATION OF THE MICROMORPHOLOGY OF THE HYBRID LAYER IN CARIES-AFFECTED DENTIN: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Conventional restorative procedures demand the inclusion of caries-affected dentin (CAD) in tooth preparation. Developments in adhesive dentistry preclude the removal of the affected layer by achieving bonding to it. This systematic review was undertaken to evaluate the micromorphology that was seen in a hybrid layer formed within CAD.

Objectives: The aim of this review was to evaluate the micromorphology of the hybrid layer in caries-affected dentin.

Material and methods: PubMed and Google Scholar databases were searched according to the inclusion and exclusion criteria from September 2010 to August 2020. References from articles were manually searched. Full-text articles available in the English language were chosen. Data extraction and quality assessment of selected articles were independently performed by two authors and a third author was consulted when needed. The risk of bias was assessed using the MINORS checklist. Data were entered in appropriate tables for assessment of obtained results.

Results: Out of the 328 search results, 325 were excluded and 3 studies were selected for inclusion in the present review. This systematic review favored sound dentin (SoD) over CAD. Morphological and chemical characteristics strongly influence the response of CAD in bonding which, regardless of the type of adhesives, demonstrates lower strength and durability than sound dentin.

Conclusions: Based on the studies included in the review, it can be concluded that despite the improvement in adhesion technology over recent decades, CAD bonding needs to be further understood and improved.

Key words: dentin, caries-affected dentin, dentin bonding agents, demineralized dentin, hybridization.

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INTRODUCTION

The sacrifice of healthy tooth tissue in order to achieve clean margins created a demand for conventional restorative materials such as dental amalgam. This wanton waste is easier to control with the rapid advances in the field of adhesive dentistry [1]. A giant stride was further taken when affected dentin was hybridized, instead of being removed. This was in tandem with the concepts of minimally invasive dentistry [2].

Preservation and inclusion of the affected dentin via hybridization lends itself to arrest of the progression of dental caries and also prevents the pulp from being

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unduly exposed to the elements of restorative materials and restorative procedures [3].

Dentin is a biologically composite material with both organic and inorganic components. Dental caries causes loss of the inorganic component and a collapse of the organic component in human dentin [4]. Caries-affected dentin (CAD) is thus composed of a collapsed matrix of collagen fibrils and loosened or missing hydroxyapatite crystals, as opposed to an active carious lesion, which is a necrotic zone of a mix of disintegrating dentinal tubules, micro-organisms and a matrix that has lost structure due to degradation by proteolytic activity of the bacteria [5].

This part of the lesion can be removed in toto. This leathery lesion conceals beneath it a zone of infection, which has depleted mineral content, but no structural loss [6]. It exhibits the presence of organisms along the length of the dentinal tubules. Abutting this zone is a zone of demineralization, where there is superficial mineral loss but all structures are intact and sterile. The zone of demineralization is the advancing zone, and ensuring this remains intact helps to protect the dental pulp [1, 6]. Due to the demineralization, the dentin in this zone tends to be more permeable and in the case of a slowly advancing carious lesion, the rate of formation of the sclerotic dentin may well match the rate of dissolution caused by dental caries [1, 7].

Bertassoni *et al.* [8], in 2012, stated that on a submicrometer scale, dentin is extremely organized with complex features and highly orchestrated protein assemblies. Infiltration of such organized and complex structures by synthetic monomers is the basis for all adhesive restorative material procedures currently found in dentistry [9]. Occupying space vacated by leached out minerals, during the process of acid etching, allows the formation of a resin-interdiffusion zone, also known as the hybrid layer [10-12]. Characteristics of the hybrid layer formed within normal, unaffected or sound dentin are well documented in the literature.

In spite of all the advances that have occurred in the field of adhesive dentistry, this bonded interface continues to significantly contribute to the failure of tooth-colored restorations [13]. This is attributed to the sorption of water into this hybridized zone [14, 15]. The presence of this water contributes to hydrolytic events at the submicrometer scale. These water molecules prevent the complete impregnation of demineralized dentin collagen by adhesive monomers [8].

The challenges faced during hybridization of caries-affected dentin (CAD) are over and above those faced during hybridization of normal dentin [7]. Integrating this organizationally sound CAD in the restorative process augurs well for the clinical outcome by reducing post-operative complications and improving the clinical prognosis.

OBJECTIVES

The objective of this systematic review was to compile all the literature available about the hybrid layer that is formed when CAD is hybridized.

MATERIAL AND METHODS

DEVELOPMENT OF PROTOCOL

The present systematic review was executed according to the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) statement 2020 and has been registered with PROSPERO (ID: CRD42020208505). A protocol including the aspects of methodology was made. The focused question that was developed was "What is the micromorphology of hybrid layer in caries-affected dentin?"

Inclusion criteria:

(P) Population: permanent human teeth with caries-affected dentin

(I) Intervention: use of bonding agent

(C) Control: not applicable

(O) Outcome: micromorphology of hybrid layer in caries-affected dentin.

(S) Study type: randomized controlled studies, controlled clinical trials, cohort studies, ex vivo studies, in vitro studies

Exclusion criteria:

Animal studies, case reports, systematic reviews, literature or scoping review, opinion articles, letters to the editor, and articles in languages other than English were excluded.

SEARCH STRATEGY

An electronic search was conducted on the PubMed database to identify the studies to be included in the review. Literature was searched for articles from September 2010 to August 2020. Forward citation tracking was conducted using Google Scholar. Manual hand search was undertaken for the reference list of eligible studies to ensure the identification of relevant published and unpublished studies. Several search terms and strategies were applied to identify studies. These include strategies to search the micromorphology of hybrid layer in caries-affected dentin. The search strategy is depicted in Table 1.

SCREENING METHOD

Two researchers (SA and PD) independently reviewed the complete list of articles and selected potentially relevant articles first by name and then by abstract. Duplicate and non-relevant articles were discarded.

TABLE 1. Search strategy

Sr. No.	Search strategy	Number of articles found	Excluded by title	Number of articles selected	Duplicates excluded	Excluded after review of full text	Final selection of articles
SS.1	Dentin AND bonding agent AND demineralized dentin AND bonding agent.	5	5	0	0	0	0
SS.2	(dentin OR CAD) AND bonding agent AND demineralized dentin AND hybridization	5	5	0	0	0	0
SS.3	Dentin AND (bonding agent OR dentin adhesive) AND demineralized dentin AND hybridization	7	5	0	0	0	0
SS.4	Dentin AND bonding agent AND (demineralized dentin OR dentin surface) AND hybridization	31	5	0	0	0	0
SS.5	Dentin AND bonding agent AND demineralized dentin AND (hybridization OR hybrid layer)	5	5	0	0	0	0
SS.6	Dentin AND bonding agent AND demineralized dentin AND (hybridization OR micromorphology)	5	5	0	0	0	0
SS.7	(dentin OR caries-affected dentin) AND dentin adhesive AND dentin surface AND (hybrid layer OR micromorphology)	5	5	0	0	0	0
SS.8	caries-affected dentin AND (dentin adhesive OR bonding agent) AND dentin surface AND (hybrid layer OR micromorphology)	2	2	0	0	0	0
SS.9	caries-affected dentin AND dentin adhesive AND (dentin surface OR demineralized dentin) AND (hybrid layer OR micromorphology)	2	2	0	0	0	0
SS.10	caries-affected dentin AND dentin adhesive AND dentin surface AND (hybrid layer OR hybridization OR micromorphology)	1	1	0	0	0	0
SS.11	Caries-affected dentin AND hybrid layer AND dentin adhesive	21	18	3	0	0	3
SS.12	Caries-affected dentin AND bonding agent AND micromorphology	3	3	0	0	0	0
SS.13	Caries-affected dentin AND dentin adhesive AND demineralized dentin AND hybridization	5	5	0	0	0	0
SS.14	Caries-affected dentin AND bonding agent AND hybrid layer	27	27	0	0	0	0
SS.15	Demineralized dentin AND bonding agent AND hybridization	90	90	0	0	0	0
SS.16	Demineralized dentin OR caries-affected dentin AND bonding agent AND hybridization	114	114	0	0	0	0
Total		328	325	3	0	0	3

The two authors independently screened the titles and abstracts of the studies for inclusion based on the question: What is the micromorphology of the hybrid layer in caries-affected dentin? In the event of discrepancies, differences were discussed until agreement was reached. A full-text screening identified articles that met the inclusion and exclusion criteria.

DATA EXTRACTION AND ANALYSIS

The data extraction was carried out by one author (SA) and later reviewed by a second author (PD); disagreements were resolved through discussion. A standardized pre-piloted form was used to extract data from the included studies for evidence synthesis. Any discrepancies were identified and resolved through discussion with the third author (RD) where necessary.

ASSESSMENT OF STUDY QUALITY

The quality of the selected studies was assessed using the methodological index for non-randomized studies (MINORS) checklist [16]. Three authors (SA, PD, RD) assessed the quality of the included studies. Based on the 12-point checklist, the response for each methodological item was answered as yes, no or not applicable. Agreement between the three raters was assessed overall using the kappa statistic.

GRADE

Relating to each outcome in the Summary of Findings, the quality of evidence was assessed using the evidence grading system GRADE as described in Section 12.2 of the Cochrane Handbook for Systematic Reviews of Interventions. The GRADE system was applied by one author and the quality of evidence for each outcome was then discussed with the other two authors. The final decision on ratings was reached by consensus. Criteria for downgrading the quality of evidence included five domains: Risk of Bias, Inconsistency of Results, Indirectness of Evidence, Imprecision of Results, and Publication Bias.

RESULTS

SEARCH OUTCOMES

Initial search results yielded 328 articles from the PubMed database. After removal of duplicates and non-relevant articles, 325 results were excluded. A total of three studies published between 2010 and 2019 were included in the present review. The PRISMA flow diagram is shown in Figure 1.

CHARACTERISTICS OF THE SELECTED STUDIES

Geographical characteristics: The studies were conducted in various countries across the globe, in the three main continents of Asia (China) [17], Europe (Italy) [18], and South America (Brazil) [19].

Study design: All studies included in the present review tested extracted teeth. Two studies evaluated bonding with carious and sound dentin on separate teeth [18, 19], whereas one study only evaluated carious teeth, where teeth were ground such that carious dentin was surrounded by sound dentin [17]. Two studies performed bonding procedures on extracted third molars [17, 19]. In one study, bonding and restorative procedures were carried out in vivo on premolars and the teeth were extracted 20 minutes after polymerization [18]. Two studies compared etch-and-rinse adhesive with self-etching adhesive [17, 19] and one study used self-etch adhesives only [18].

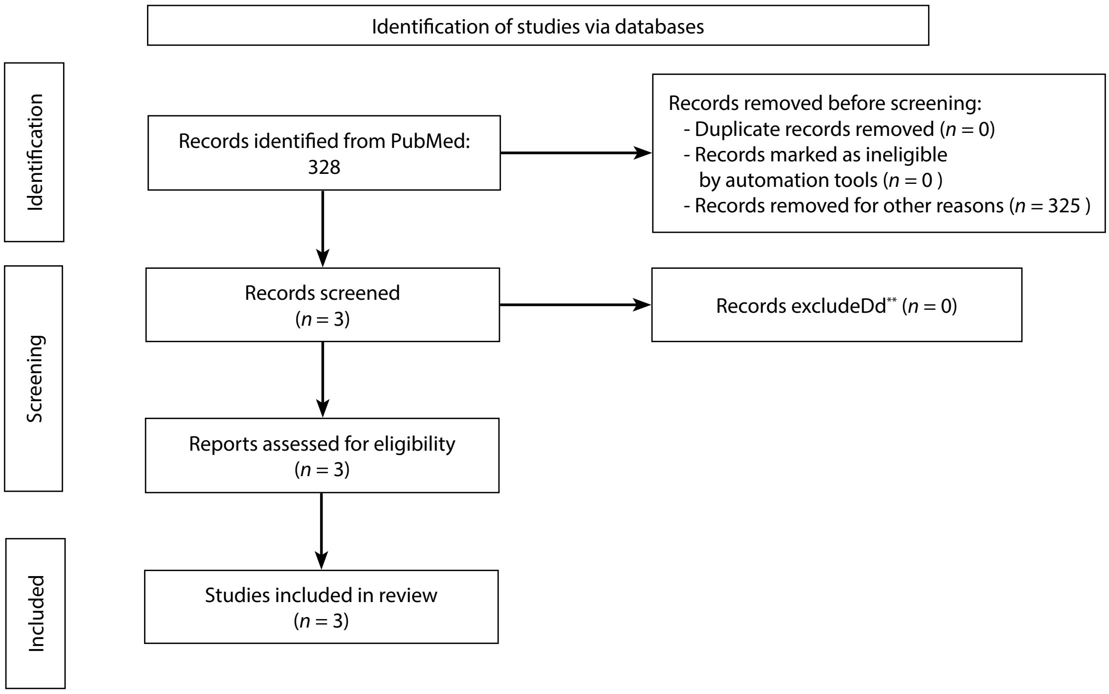
Xuan *et al.* [17] compared the micromorphology and bond strengths of etch-and-rinse adhesive Adper Single Bond 2 with self-etching adhesive Clearfill SE bond, Clearfill S3 bond and iBond GI. The researchers used teeth with coronal caries, extending halfway through the dentin. The CAD was isolated with filing and caries detection dyes. The tooth substrate was dissolved by immersion in HCl acid, followed by exposure to 5% NaOCl to dissolve any remnants of collagen fibrils. Milia *et al.* [18] analyzed the hybrid layer formation after application of a self-etching system to CAD and SoD. The adhesives used were Clearfil S^3 bond, a self-etch adhesive, and Clearfil Protect Bond (2 step with primer in the first step and adhesive in the second step). Hass *et al.* [19] examined the bonding performance of Scotchbond Universal (3M Oral Care, St. Paul, MN, USA, also known as Single Bond Universal in some countries), Futurabond Universal (Voco, Cuxhaven, Germany), and Prime&Bond Elect (Dentsply Caulk, Konstanz, Germany).

OUTCOME ASSESSMENT

Two studies tested the microtensile bond strength using a universal testing machine and the morphological features of the hybrid layer were evaluated using a scanning electron microscope [17, 19]. One study used transmission electron microscopy (TEM) [18]. One study also evaluated the in situ degree of conversion, tested using micro-Raman spectroscopy [19].

CHARACTERISTICS OF OUTCOMES

All studies included in the review found that hybrid layers were uniformly formed, with higher integrity and longer resin tags in sound dentin and that the hybrid layer was thicker in caries-affected dentin for all bonding strategies, but the resin tags were shorter with irregular shape [17-19].



Source: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. DOI: 10.1136/bmj.n71

FIGURE 1. PRISMA 2020 flow diagram

TABLE 2. Risk of bias assessment

SR. No	Methodological items	Xuan *et al.*	Milia *et al.*	Hass *et al.*
1.	Clearly stated aim	Yes	Yes	Yes
2.	Inclusion of consecutive patients	NA	NA	NA
3.	Prospective collection of data	Yes	Yes	Yes
4.	Endpoints appropriate to the aim of study	Yes	Yes	Yes
5.	Unbiassed assessment of the study endpoint	Yes	Yes	Yes
6.	Follow-up period appropriate to end of the study	NA	NA	NA
7.	Loss of follow-up less than 5%	NA	NA	NA
8.	Prospective calculation of study size	NA	NA	NA
9.	Adequate control group	Yes	Yes	Yes
10.	Contemporary groups	Yes	Yes	Yes
11.	Baseline equivalence of groups	Yes	Yes	Yes
12.	Adequate statistical analysis	Yes	Yes	Yes

One study found that the resin tags of the etch-and-rinse adhesives were funnel shaped with lateral branches and cylindrical in shape and slender for self-etching adhesives [17].

Milia *et al.* [18] found that the one-step self-etch S3 bond formed an uneven hybrid layer in CAD, with lesser occlusion of the dentinal tubules and more homogeneous reinforcement. Morphology of the hybrid layer mirrored that of the dentin characteristics. Morphological movement of fluids was not observed in CAD, whereas high permeability was seen in the intratubular space of sound dentin and within the hybrid layer. In carious dentin, the two-step P bond self-etch adhesive formed a hybrid layer consisting of a thick various smear layer and dentin subsurface that formed tubular resin plugs with no void formation. In sound dentin, areas of porosities were seen in peritubular regions [18].

Hass *et al.* [19] found that the resin tag formation in sound dentin was more evident for self-etch resins. They reported that collagen fibrils were collapsed with

TABLE 3. Comparison of number, length and thickness of resin tags

Authors (year)	Intervention	Resin tag thickness	Resin tag no	Resin tag length
Xuan *et al.* (2010)	M Single Bond 2 (SB2) or self-etching adhesives Clearfil SE Bond (CSE), Clearfil S^3 Bond (CS^3), iBond GI (IB)	The hybrid layers in caries-affected dentin were thicker compared to those in normal dentin for all the testing adhesives.	N/A	(FOR NORMAL DENTIN) 1. The hybrid layer formed after the application of the E&R adhesive Single Bond 2 was 4 μm, the thickest of all the 4 adhesives. 2. For the SE group, Clearfil SE Bond generated a hybrid layer of 1 μm, Clearfil S^3 Bond led to the formation of the thinnest hybrid layer, which was less than 1 μm.
Milia *et al.* (2012)	Clearfil S^3 Bond, Clearfil Protect Bond (Pbond)	The study concluded that the hybrid layer was thicker in CAD as compared to sound dentin.	N/A	1. The hybrid layer of CAD in Clearfil S^3 bond had a thickness of 2.2 μm while in sound dentin it was thin – 0.5 μm (approx.) 2. In Pbond the hybrid layer in CAD had a thickness of 4 μm in depth and in sound dentin it was thin, about 0.5 μm in depth.
Hass *et al.* (2019)	Scotchbond Universal (SBU), Futurabond U (FBU), and Prime & Bond Elect (PBE)		When using the etch-and-rinse mode for the CAD substrate, PBE demonstrated minimal resin tag formation, while resin tags were mostly absent when using the self-etch mode.	CAD images presented hybrid layers with scarce and incomplete tag formation for all adhesive systems. FBU demonstrated few and short needle-like resin tags within the CAD substrate, although with a higher intensity than PBE.

more porosity signals, and resin tags were almost absent in Prime&Bond Elect adhesive. Futurabond U adhesive formed lesser and shorter needle-like resin tags with CAD. Prime&Bond Elect adhesive used with the etch-and-rinse strategy in CAD formed minimal resin tags. Table 2 summarizes the characteristics of individual studies.

QUALITY ASSESSMENT

The risk of bias in the selected studies was assessed using the MINORS checklist [16]. Based on the 12-point checklist, the response for each methodological item was answered as yes, no or not applicable. The response to each item is tabulated in Table 3.

QUALITY OF EVIDENCE

The present review included three studies with a total sample size of 120 teeth. The studies evaluated bonding with carious and sound dentin on separate teeth [18, 19], as well as on carious teeth, where teeth were ground such that carious dentin was surrounded by sound dentin [17]. Though the methods of assessment were different, the results of all the studies were relatively similar. No serious risk of bias, inconsistency, imprecision, indirectness or publication bias was observed in the included studies. Since all the included studies are *in vitro* or *ex vivo*, our confidence in the estimated effect remains limited.

DISCUSSION

Caries affects both the organic and inorganic phases of dentin [7]. At the sub-micrometer scale, in the mineral phase, CAD shows a reduction in Mg content. At this stage the lesion is still reversible, before the decrease in Ca and P content starts. The mineral crystals in CAD show scattered and random distribution with wider spaces as opposed to intact dentin [20]. In the organic phase, there is a reduction of the intermolecular cross links in the collagen – a change which is still reversible [21]. Once the secondary structure of enamel, i.e. the complex arrangement of its constituent proteins, is disturbed, the change then becomes irreversible [22].

The carious process leads to occlusion of the tubular lumen by minerals made up of large rhombohedral crystals of Mg-substituted B-TCP (whitlockite) [23], which is less soluble than hydroxyapatite. Within the dentin matrix the mineral that is lost is replaced by water. Thus, sound dentin has a water content of approximately 10%, whereas CAD shows the presence of water in the range of 14-53%. This increased water level adversely affects the mechanical properties of CAD, making it softer than SoD [4, 24-29]. The ultimate tensile strength (UTS) of adhesive restorations in CAD is significantly lower than that in SoD.

SUMMARY OF FINDINGS

Xuan *et al.* [17] explained the morphology of the hybrid layer in CAD, the partially demineralized nature of inter-tubular dentin and consequent deeper monomer infiltration in normal dentin. But they did not identify any correlation between hybrid layer thickness, resin tag length and bond strength.

Milia *et al.* [18] evaluated the morphological characterization using TEM to analyze the hybrid layer formation after application of a self-etching system to CAD and SoD. They contended that the permeability of deep sound dentin was likely to generate greater water movement. In contrast, in CAD because of the occlusion of dentinal tubules, there is restricted movement of water [18]. They further stated that it was improbable to clinically achieve a base of CAD and no other dentinal type was involved. Clinicians have to deal with varying degrees of tubular occlusion and differing dentin morphologies in the same cavity [30-32].

Hass *et al.* [19] in 2019 examined the bonding performance of etch and rinse and self-etch strategies during the application of universal adhesive systems. They examined several features of the adhesives: microtensile bond strength (μTBS), degree of conversion within the hybrid layer (DC) and a thorough morphologic analysis of the hybrid layer. SEM analysis of the hybrid layer showed high integrity in sound dentin. The resin tags in SoD were greater in number and longer compared to those seen in CAD. They also established that these features occurred more in the etch and rinse technique than the self-etch technique. Thus, the best hybrid layer was found in SoD, where the adhesives had been applied with the etch and rinse technique. On the other hand, SEM images of CAD showed hybrid layers with little to no tag formation for all the adhesive systems, irrespective of the strategy used.

OVERALL COMPLETENESS AND APPLICABILITY

The study by Milia *et al.* [18] was unique in the fact that they studied the micromorphology of the hybridized tissue, in SOD, deep sound dentin (DSD) and CAD simultaneously in the same tooth. Their study was carried out on carious and non-carious teeth destined for extraction, using a transmission electron microscope (TEM), as the TEM could potentially evaluate the sub-micron thickness of the hydrophilic hybrid layer. They compared this against the hybrid layer formed by a hydrophobic, self-etching adhesive, in the same simulation. The adhesives used were Clearfil S^3 bond, a self-etch adhesive and Clearfil Protect Bond (2 step with primer in the first step and adhesive in the second step). Milia *et al.* [18] claim to have been the first to analyze, in a clinical situation, the formation of a hybrid layer in CAD and DSD. This could possibly explain the water tree formation and the water voids, as the adhesives respond to the water movement in the vital dentin. This could lead to hydrolytic degeneration of the bonds and subsequent clinical failure. The thickness of the hybrid layer achieved could, in the clinical scenario, allow for the bonding of the CAD, as opposed to its removal [33-36].

Hass *et al.* [19] evaluated both tensile bond strength and micro-morphology of the hybrid layer and were able to conclusively state that, irrespective of the adhesive system or the technique used, the bond strength was significantly lower in CAD. These results could be explained by the dynamic events that are associated with the caries process, mineral loss and gradual deterioration of the dentinal tubules [37]. These events caused increased porosities in the inter-tubular dentin which affected the hybridization of CAD [38]. These translate into reduced bio-mechanical properties for CAD. Hass *et al.* [19] inferred that the tubular blockage and presence of an acid-resistant intra-tubular mineral deposit in CAD interferes with the monomer penetration. They also explained that to evaluate the effect of the caries process on bonding with carious dentin at various levels, isolated lesions should be studied. However, various experimental designs have reported impaired bonding with carious dentin, indicating that carious dentin at any level has lower bond strength compared to sound dentin. Their conclusion was in accordance with previous studies, in which artificial caries protocols were employed in both deciduous and permanent teeth [39-43]. Even though these protocols do not simulate the cascade of events involved in natural caries exactly, they do provide isolated alterations in the dentinal substrate [19]. There are reports that the mechanical properties of the matrix of demineralized CAD remained unaffected [44]. This could be explained by the loss of mineral in inter-tubular dentin. In arrested caries, the transparent layer of CAD showed similar properties to the underlying SoD [28, 29].

The smear layer of CAD appears thicker and had a larger proportion of organic components, as compared to SoD [44, 45]. Given that CAD has altered mechanical properties, the resultant mechanical properties of the adhesive layer too would be altered [24-26, 45-55]. The hybrid layer formed in CAD shows a higher amount of cohesive failure secondary to a reduction in cohesive strength [15]. This reduction was found to occur regardless of the type of adhesive system used (etch and rinse system or self-etch system; one/two/three step bonding procedure) [24-26, 45-57].

LIMITATIONS AND STRENGTHS

To prevent any bias in selection of studies, multiple authors assessed the eligibility of search results independently using strict inclusion and exclusion criteria. Only full-text articles available in English language were included, which excluded papers published in any other language. Nevertheless, there are some limitations in the present review. The majority of the papers are *in vitro* studies and do not provide key information required for quality assessment. In the included studies, the methodology and bonding strategy in each study differed. There are no clinical studies providing long term data evaluating this treatment concept. Further in-depth analysis through randomized controlled trials using multiple uniform established protocols and parameters is necessary.

CONCLUSIONS

This systematic review evaluated the micromorphology of the hybrid layer in caries-affected dentin. Three studies evaluating bonding in extracted teeth were included in the review. The data of this systematic review show that the hybrid layer formed in CAD is thicker than sound dentin, with little to no resin tag formation. The physiological movement of fluids in the dentinal tubules is also restricted in CAD. Within the limitations of the present review, it can be concluded that bonding to caries-affected dentin leads to a reduction of the bond strengths, where etch-and-rinse technique showed better results than self-etch technique, which were not significantly different. Though the bond strength is lower, bonding with caries-affected dentin precludes injury to the pulp vitality.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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