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Lucas Spat Javorsky

**INFLUÊNCIA DA REMOÇÃO QUÍMICO-MECÂNICA DE TECIDO  
CARIADO NA ADESÃO À DENTINA: REVISÃO SISTEMÁTICA E  
META-ANALISE**

Santa Maria, RS  
2021

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ADESÃO À DENTINA: REVISÃO SISTEMÁTICA E META-ANALISE**

Dissertação apresentada do Programa de Pós-Graduação em Ciências Odontológicas, Área de Concentração em Odontologia, ênfase em Odontopediatria, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para a obtenção do título de **Mestre em Ciências Odontológicas**.

Orientadora: Prof. Dr. Rachel de Oliveira Rocha

Santa Maria, RS  
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**Lucas Spat Javorsky**

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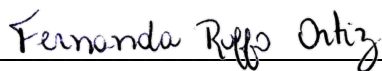
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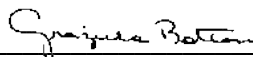
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## DEDICATÓRIA

*Dedico este trabalho a toda minha família que sempre me forneceu todo suporte e todo amor necessário para chegar até aqui. Em especial, para minha mãe, professora que sempre lutou pela educação, e ao meu pai, funcionário público, que se dedicou por tanto tempo a essa instituição.*

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## RESUMO

### INFLUÊNCIA DA REMOÇÃO QUÍMICO-MECÂNICA DO TECIDO CARIADO, NA ADESÃO À DENTINA: REVISÃO SISTEMÁTICA E META-ANÁLISE

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Os agentes de remoção químico-mecânica de tecido cariado foram desenvolvidos na intenção de facilitar o procedimento, tornando-o mais conservador e amigável ao paciente. No entanto, não há consenso na literatura acerca da sua influência na adesão à dentina previamente tratada. Assim, este estudo, que tem como objetivo revisar sistematicamente a literatura para estudos laboratoriais que avaliaram a influência do uso de agentes de remoção químico-mecânica de tecido cariado na adesão à dentina. A busca por estudos laboratoriais foi realizada nas bases de dados eletrônicas (PubMed, Scopus, ISI Web of Science e LILACS) a partir da estratégia criada pela combinação de termos específicos (MeSH) e termos livres, sem limite de data ou idioma. Os estudos foram selecionados segundo o critério de inclusão: 1) ter comparado o método de remoção químico-mecânica de tecido cariado com o método convencional (com instrumentos manuais e rotatórios); 2) ter avaliado a resistência de união de sistemas adesivos. Após a leitura integral, os estudos que não apresentaram valores de resistência de união como médias e desvio-padrão, realizaram a avaliação em dentina hígida ou que utilizaram agentes de remoção químico-mecânica ou sistemas adesivos não disponíveis comercialmente (experimentais) foram excluídos. Dois revisores selecionaram os estudos, extraíram os dados e avaliaram o risco de viés. Foram identificados 695 estudos, dos quais 102 constavam em mais de uma base (duplicatas). Assim, 593 estudos foram submetidos a avaliação inicial, dos quais 39 preencheram os critérios de inclusão. Destes, 26 foram incluídos na revisão sistemática e meta-análise. A remoção químico-mecânica de tecido cariado não impactou os valores de resistência de união a dentina ( $Z=0,52$ ;  $p=0,61$ ), independente do agente ( $Z=0,64$ ;  $p=0,52$ ) ou estratégia do sistema adesivo ( $Z=0,44$ ;  $p=0,66$ ). Em dentes decíduos, a remoção químico-mecânica reduziu os valores de resistência de união ( $Z=2,21$ ;  $p=0,03$ ). A maioria dos estudos apresentou moderado risco de viés. Esta revisão sistemática e meta-análise demonstrou que a remoção químico-mecânica de tecido cariado não influencia a resistência de união de sistemas adesivos à dentina, exceto em dentes decíduos.

**Palavras-chave:** Adesivos Dentinários. Dentina. Resistência à Tração

## ABSTRACT

### INFLUENCE OF CHEMOMECHANICAL CARIES REMOVAL ON DENTIN BOND STRENGTH: SYSTEMATIC REVIEW AND META-ANALYSIS

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The chemomechanical caries removal agents were developed to facilitating the procedure, making it more conservative and patient-friendly. However, there is no consensus in the literature about their influence on bonding to previously treated dentin. Thus, this study aimed to systematically review the literature for laboratory studies that evaluated the influence of chemomechanical caries removal agents on bonding to dentin. The search for laboratory studies was performed in electronic databases (PubMed, Scopus, ISI Web of Science, and LILACS) using a strategy created by combining specific terms (MeSH) and free terms, with no date or language limitation. The studies were selected according to the inclusion criteria: 1) comparing the chemomechanical caries removal and conventional method, and 2) evaluating the bond strength of adhesive systems. After full-text reading, studies that did not present bond strength values as means and standard deviation, performed the evaluation on sound dentin, or used chemomechanical agents or adhesive systems not commercially available (experimental) were excluded. Two reviewers screened the studies, extracted the data, and assessed the risk of bias. A total of 695 studies were identified, of which 102 were in more than one database (duplicates). Thus, 593 studies were submitted for initial evaluation, of which 39 met the inclusion criteria. Of these, 26 were included in the systematic review and meta-analysis. Chemomechanical caries removal did not impact bond strength values ( $Z=0.52$ ;  $p=0.61$ ), regardless of agent ( $Z=0.64$ ;  $p=0.52$ ) or adhesive system strategy ( $Z=0.44$ ;  $p=0.66$ ). On primary teeth, chemomechanical caries removal agents reduced the bond strength values ( $Z=2.21$ ;  $p=0.03$ ). Most studies presented a moderate risk of bias. This systematic review and meta-analysis demonstrated that chemomechanical caries removal does not influence the bond strength of adhesive systems to dentin, except on primary teeth.

**Keywords:** Dentin-Bonding Agents. Dentin. Tensile strength.



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## 1 INTRODUÇÃO

A remoção seletiva de tecido cariado tem sido considerada a conduta mais apropriada para lesões de cárie profundas a fim de reduzir o risco de exposição pulpar e sintomatologia pós-operatória (EMARA; KROIS; SCHWENDICKE, 2020; SCHWENDICK; DÖRFER; PARIS, 2013). Apesar disso, os parâmetros clínicos de consistência e coloração, considerados como guias durante a remoção seletiva, são subjetivos e podem acarretar na remoção aumentada e desnecessária de parte da dentina (BANERJEE; KIDD; WATSON, 2003), aumentando assim o risco de exposição pulpar.

O desenvolvimento de agentes de remoção químico-mecânica de dentina cariada desde a década de 80, foi impulsionado pela intenção de facilitar o procedimento, pela atribuída ação seletiva dos agentes químicos. O produto pioneiro, denominado Caridex™, foi substituído, no final dos anos 90, pelo produto Carisolv™, composto por hipoclorito de sódio e aminoácidos específicos, atuando na degradação do colágeno da dentina cariada (ação química) associados a remoção mecânica, por raspagem, com o uso de instrumentos específicos (curetas sem corte) (ERICSON *et al.*, 1999; FURE; LINGSTRÖM, 2004). Outro produto mais recente, à base de papaína, enzima extraída do mamão, comercializado a partir de 2003 com o nome de PapaCárie®, da mesma forma que o anterior, tem sua ação fundamentada na ação proteolítica da enzima que o compõe.

A remoção químico-mecânica da dentina cariada geralmente dispensa a necessidade de anestesia local e, mesmo que o tempo consumido seja superior quando do uso da técnica convencional com instrumento rotatório (HOSEIN; HASAN, 2008) representa maior conforto ao paciente pela ausência da vibração decorrente do uso de brocas em baixa velocidade. É preciso considerar, no entanto, que o uso de agentes para a remoção químico-mecânica da dentina cariada, dada sua ação primordial sobre o colágeno, presente abundantemente na dentina afetada, pode resultar na remoção desnecessária de dentina cariada (HOSSAIN *et al.*, 2003), com similar risco de complicações ao método tradicional (SCHWENDICKE; PARIS; TU, 2015) e ainda, comprometer a adesão ao substrato dentinário previamente tratado (CEBE *et al.*, 2016; FAUSTINO-SILVA *et al.*, 2009; SIRIN KARAARSLAN *et al.*, 2012).

A influência do uso de agentes químico-mecânicos para remoção de dentina cariada na adesão ainda não está clara, dado que alguns estudos apontam valores superiores de resistência de união (EL-KHOLANY *et al.*, 2005; NAIK *et al.*, 2014; NEVES *et al.*, 2011) ou ainda similares quando da comparação com a remoção convencional (HAMAMA; YIU; BURROW, 2015; BOTELHO-AMARAL *et al.*, 2011). Considerando que procedimentos simplificados, que favoreçam o controle do comportamento infantil sejam desejáveis em Odontopediatria e

ainda, que as revisões sistemáticas são ferramentas fundamentais no processo de tomada de decisão, este estudo tem como objetivo revisar sistematicamente a literatura para estudos laboratoriais que avaliaram a influência da remoção químico-mecânica de tecido cariado na resistência de união de sistemas adesivos à dentina.

## **2 ARTIGO - INFLUENCE OF CHEMOMECHANICAL CARRIES REMOVAL ON DENTIN BOND STRENGTH: SYSTEMATIC REVIEW AND META-ANALYSIS**

O presente trabalho está apresentado na forma artigo, redigido conforme as normas do periódico *International Journal of Paediatric Dentistry* (ISSN 1365-263X); Qualis CAPES Quadriênio 2013-2016 - A1.

**Article type:** Systematic review

**Influence of chemomechanical caries removal on dentin bond strength: Systematic review and Meta-analysis.**

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ROR conceived the idea and study design. LSJ and ROR performed the literature search.

ROR performed the extraction of data and the meta-analysis. LSJ wrote the manuscript. ROR and FZMS contributed substantially to discussion and proofread the manuscript before its submission.

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## **Influence of chemomechanical caries removal on dentin bond strength: Systematic review and Meta-analysis.**

### **ABSTRACT**

**Background:** The impact of chemomechanical caries removal on adhesive systems bonding to dentin is unclear.

**Aim:** To systematically review the literature of in vitro studies regarding the influence of chemomechanical caries removal on the bond strength values of adhesive systems to dentin.

**Design:** The electronic databases PubMed, Web of Science, Scopus, and LILACS were considered to search studies comparing the bond strength of adhesive systems to dentin subjected to chemomechanical or conventional (rotary or manual excavation). Two reviewers independently selected the studies, one extracted the data, and evaluated the risk of bias. The bond strength data were meta-analyzed using a random-effects model, with a significance level of  $p < 0.05$ . Heterogeneity ( $I^2$ ) was assessed by the Cochran Q test.

**Results:** From 695 screened studies, 39 reports were assessed for eligibility, and 26 were included in the systematic review and meta-analysis. Chemomechanical caries removal did not impact on bond strength values ( $Z=0.52$ ;  $p=0.61$ ), regardless the agent ( $Z=0.64$ ;  $p=0.52$ ) or adhesive etching strategy ( $Z=0.44$ ;  $p=0.66$ ). Chemomechanical caries removal jeopardized the bonding to primary dentin ( $Z=2.21$ ;  $p=0.03$ ). Most of the studies presented a moderate risk of bias.

**Conclusion:** Chemomechanical caries removal does not impact the bond strength of adhesive systems, except in primary dentin.

**Keywords:** adhesive system; systematic review; dentin; chemomechanical agents.

## 1. INTRODUCTION

Selective removal of carious dentin is the preferred procedure for managing the deep caries lesions, reducing the risk of pulpal exposure and postoperative symptoms in both primary and permanent teeth.<sup>1,2</sup> However, visual and tactile parameters of dentin as color, moisture, and hardness, to define the endpoint of carious dentin removal, are subjective and may lead to increased and unnecessary removal of dentin,<sup>3</sup> thus increasing the risk of pulpal exposure.

Chemomechanical agents for carious dentin removal were introduced to minimize the excessive tissue removal<sup>4</sup> by the selective action of chemical components. Carisolv™ replaced the first developed agent named Caridex™, which is a gel composed of sodium hypochlorite and specific amino acids (glutamic acid, leucine, and lysine), with collagenolytic activity, acting only on infected dentin, preserving affected dentin.<sup>5,6</sup> Another available agent, Papacarie, is mainly based on papain, an enzyme extracted from papaya peel and chloramine, chemically breaking denatured collagen fibers and softening carious dentin, making it easier to remove decayed tissue. In general, chemomechanical agents, although requiring longer clinical time, are less painful, no vibration, do not require local anesthesia, being more patient-friendly.<sup>7,8</sup>

It should be considered, however, that the use of agents for the chemomechanical removal of carious dentin, given its primary action on collagen, abundantly present in the affected dentin, may result in unnecessary tissue removal,<sup>9</sup> increasing the risk of pulpal damage<sup>10</sup> and also, compromise the adhesion to the previously treated dentin.<sup>11,12,13</sup>

The chemomechanical agents effect on dentin bonding is still unclear, as some studies show higher values of bond strength<sup>14-16</sup> or even similar when compared with conventional caries removal (using rotary or manual instruments).<sup>17,18</sup> In Pediatric Dentistry, simplified restorative procedures favor the children's behavior control and are always preferable, as long as they are comparable to conventional ones, in terms of pulp damage and restoration longevity.

Furthermore, systematic reviews are fundamental tools in the decision-making process; thus, this study aimed to systematically review the literature for laboratory studies that evaluated the influence of chemomechanical caries removal on the bond strength of adhesive systems to dentin. The tested null hypothesis was that chemomechanical caries removal does not influence the bond strength values of adhesive systems to dentin.

## **2. MATERIALS AND METHODS**

The Cochrane Handbook<sup>19</sup> and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)<sup>20</sup> were used as a guide to conduct and report this systematic review. The research PICO question was: "Does chemomechanical caries removal influence on dentin bond strength?"; in which the dentin was the 'population'; chemomechanical caries removal was the 'intervention'; manual or rotary caries removal was the 'control', and bond strength was the 'outcome'.

### **2.1 Search strategy**

Four electronic databases PubMed/MEDLINE, SCOPUS, ISI Web of Science, and LILACS were searched to identify literature up to June 2021 related to the research question. For PubMed/MEDLINE a search strategy was developed by combining controlled vocabulary (Mesh terms) and free terms as follow: (((((((((((carisolv[Supplementary Concept]) OR (carisolv)) OR (papacarie[Supplementary Concept])) OR (papacarie)) OR (papacárie)) OR (chemomechanical)) OR (chemomechanical\*)) OR (chemo-mechanical)) OR (chemo-mechanical\*)) AND (((((((((((conventional caries removal) OR (caries removal)) OR (dentin



removal)) OR (dentin\* removal)) OR (dentin excavation)) OR (dentin\* excavation)) OR (caries excavation)) OR (cari\* removal)) OR (cari\* excavation)) OR (rotary instrument)) OR (rotary instrument\*)) OR (hand instrument)) OR (hand instrument\*)) OR (drilling))) AND (((((((((((tensile strength[MeSH Terms]) OR (tensile strength)) OR (shear strength[MeSH Terms])) OR (shear strength)) OR (tensile)) OR (shear)) OR (microtensile)) OR (micro tensile)) OR (microshear)) OR (micro shear)) OR (bond strength)) OR (bond\*))). This search strategy was adapted for SCOPUS considering the terms “chemomechanical” OR “papacarie” OR “carisolv” AND “bond strength”. The terms “chemomechanical\*caries” OR “Carisolv” OR “papacarie” AND “bond strength” were considered for searching in ISI Web of Science. For LILACS, the terms (papacarie) OR (carisolv) AND (bond) were used. No language or publication date restrictions were considered in the search. Search results were collected in an electronic spreadsheet (Numbers 11.1, Apple Inc, Cupertino, CA, USA) and manually cross-checked to eliminate duplicates.

## **2.2 Study selection, inclusion, and exclusion criteria**

According to the eligibility criteria, the title and abstracts of each reference were independently screened by two trained and calibrated reviewers (L.S.J.and R.O.R) (Kappa= 0.82): chemomechanical compared to conventional caries removal on the bond strength of adhesive systems to dentin. Disagreements were solved by consensus or with a third reviewer's judgment (F.Z.M.S.).

The full text of the studies selected was retrieved and screened by the two reviewers using the exclusion criteria: 1) chemomechanical removal agent or adhesive system not commercially available (experimental); 2) no bond strength values as means and standard

deviation; 3) evaluation on sound dentin. In addition, the reference lists of the selected studies were manually screened to identify studies not registered in the search databases.

### **2.3 Data extraction**

The data contained in the included studies were extracted by one researcher (R.O.R.), using a predefining collection form (Numbers 11.1, Apple Inc, Cupertino, CA, USA), including first author name, year of publication, country of the first author, tooth type, number of teeth in each experimental group, chemomechanical agent (commercial brand), conventional caries removal, adhesive systems (commercial brand), bond strength test, and bond strength values (means and standard deviations). To obtain unclearly or missed data, authors were contacted by email. Studies reporting the same bond strength data were considered only once.

### **2.4 Assessment of risk of bias**

The methodological quality of the included studies was assessed by a risk of bias criteria, adapted from a previous systematic review<sup>26</sup> including the following items: sample size calculation, the same number of teeth in each experimental group, random sequence for specimens preparation, chemomechanical caries removal agent and adhesive systems used according to the manufacturer's instructions, a single operator responsible for caries removal and adhesive procedures, failure mode evaluation, and blinding of the operator responsible for the outcome analysis. Studies with a clear description of each item received a 'YES', and if the information was not presented or unclear, received a 'NO'. Studies that received 6 or 7 'YES' were judged to be a low risk of bias; a score of 4 and 5 'YES' indicates a medium risk, and a score of 1 and 2, high risk of bias.

## 2.5 Data analysis

Meta-analysis was undertaken using the inverse of variances (Z test) with a random-effects model and a significance level of 5%. For the studies that considered more than one chemomechanical agent or more than one adhesive system, the data were grouped, as mean and standard deviation, using a predefined formula<sup>19</sup>. In addition, subgroup analyses were performed considering the chemomechanical caries removal agent, adhesive system strategy (etch-and-rinse and self-etch), and primary teeth.

Inconsistency (heterogeneity) ( $I^2$ ) among studies was assessed by  $I^2$  statistics. Values higher than 50% were considered heterogeneous.<sup>19</sup> Cochran's Q statistic was used to quantify heterogeneity. All analyses were performed using Review Manager software (RevMan version 5.3; Cochrane Collaboration, London, UK).

## 3. RESULTS

### 3.1 Study selection

This systematic review initially identified 695 records from the four databases (72 from PubMed, 442 from Scopus, 171 from Web of Science, and 10 from LILACS). After subtraction of duplicates (102 records), the title and abstract of 593 studies were reviewed, and 554 studies were deemed ineligible and were excluded because they were not relevant. The full text of 39 studies was assessed, and thirteen studies were excluded. The remaining twenty-six studies were included in the systematic review and meta-analysis. The study selection process as a PRISMA flowchart is shown in Figure 1.

### 3.2 Study characteristics

The descriptive data of included studies are summarized in Table 1. The studies were from eleven countries, mainly from Brazil (7 studies),<sup>12,16,18,22-25</sup> India (5 studies),<sup>15,26-29</sup> and Turkey (4 studies).<sup>11,13,30,31</sup> Most of studies were published in English (23 studies)<sup>11,13-16,18,22,23,25-31,34,-39</sup> while 2 studies were published in Spanish<sup>32,33</sup> and one in Portuguese.<sup>12</sup> The studies were published between 2000 and 2018.

Only human teeth were used, and in five studies,<sup>12,28,32,38,39</sup> primary teeth were evaluated. Natural carious dentin was the substrate in 23 studies. One study considered artificially carious dentin by in situ induction as substrate,<sup>18</sup> and two studies used pH cycling to create artificially demineralized dentin.<sup>22,23</sup> The most evaluated chemomechanical caries removal agents were Carisolv and Papacarie. Carie-care was evaluated in two studies<sup>27,29</sup> and SFC-V (Biosolv) in one study.<sup>34</sup> Hand excavators and round burs (carbide, steel, or diamond) in slow-speed or high-speed handpiece were used in control groups. Visual, tactile and laser fluorescence methods were used as caries removal endpoint.

Seventeen adhesive systems were evaluated, both etch-and-rinse as self-etch. Adper Single Bond (3M Oral Care) was evaluated in twelve studies.<sup>12,13,18,22,23,26,27,29,30-32,38</sup> Microtensile bond strength test was the mechanical test most used (22 studies). Tensile<sup>32</sup> and shear bond strength<sup>23,28,35</sup> tests were also used.

### 3.3 Risk of bias assessment

Sixteen studies were judged as moderate risk of bias,<sup>11,13,14,16-18,22-24,27,29,30,31,35,36,38</sup> eight as high risk<sup>12,15,25,26,28,32,33,39</sup> and only two studies were classified as low risk of bias.<sup>34,37</sup> A lack of information about sample size calculation, a single operator responsible for caries removal and adhesive procedures, and blinding the operator responsible for the outcome analysis were not observed in most studies. The risk of bias assessment for the included studies is displayed

in Table 2.

### 3.4 Meta-analysis

The twenty-six included studies were considered in the overall meta-analysis (Figure 2). The overall effect was not statistically significant ( $Z=0.52$ ;  $p=0.61$ ), i.e., chemomechanical caries removal did not impact adhesive systems' bond strength to dentin. The meta-analysis resulted in significant heterogeneity ( $I^2=74\%$ ;  $p<0.00001$ ).

Subgroup meta-analysis considering Carisolv and Papacarie separately (Figure 3) also did not significantly impact on bonding regardless of the chemomechanical agent ( $Z=0.32$ ;  $p=0.75$  and  $Z=0.70$ ;  $p=0.48$ ; respectively). Heterogeneity was also observed for the two subgroups ( $I^2=74\%$ ;  $p<0.00001$  and  $I^2=76\%$ ;  $p<0.00001$ ). Furthermore, chemomechanical caries removal did not impact adhesive systems' bond strength to dentin regardless of the etching mode, as depicted in Figure 4 ( $Z=0.44$ ;  $p=0.66$ ). Significant heterogeneity was also observed in this subgroup meta-analysis ( $I^2=68\%$ ;  $p<0.00001$ ). Five studies reported the bond strength of adhesive systems to primary dentin. The subgroup meta-analysis demonstrated higher bond strength values for conventional than chemomechanical caries removal ( $Z=2.21$ ;  $p=0.03$ ). The results indicated significant heterogeneity across the studies ( $I^2=89\%$ ;  $p<0.00001$ ).

## 4. DISCUSSION

This systematic review demonstrated that chemomechanical caries removal did not impact the bond strength of adhesive systems to dentin except for primary dentin. Thus, the hypothesis that there is no influence of chemomechanical caries removal on dentin bonding must be partially accepted.

A recently published systematic review<sup>40</sup> pointed out the beneficial effects of chemomechanical caries removal regarding less pain and patient acceptance. In addition, in

pediatric patients, chemomechanical caries removal offers the advantages of no noise and vibration and often dispensing local anesthesia,<sup>38</sup> thus being very attractive. However, other aspects need to be considered when chemomechanical agents are used. Bonding to dentin depends on the morphological characteristics of this substrate that can play a role in resin monomers infiltration.<sup>41</sup> In general, after the use of chemomechanical agents, dentin presents irregular surface, amorphous layer similar to smear layer, and a small number of exposed dentinal tubules,<sup>42</sup> although each chemomechanical agent left the dentin with different characteristics.<sup>34</sup> However, the influence of these characteristics on bonding is unclear. Many studies have been conducted on chemomechanical caries removal effect on the bonding to caries-affected dentin, showing no impact on bond strength values,<sup>18,26,29,36</sup> negative effect<sup>34</sup> or even improving the bonding to dentin.<sup>14,15</sup> The overall results of this systematic review did not highlight significant differences in bond strength values comparing conventional and chemomechanical caries removal, regardless of the chemomechanical agent or adhesive system's etching strategy.

The included studies compared four chemomechanical agents, however Carisolv and Papacarie were considered in 14<sup>11,13,14-16,25,26,30,31,34,35-38</sup> and 7 studies,<sup>18,22-24,28,33,39</sup> respectively, and four studies<sup>12,17,29,32</sup> compared both Carisolv and Papacarie to conventional caries removal. Thus, the agents Cari-Care<sup>27,29</sup> and SFC-V (Biosolv)<sup>34</sup> were compared by only 2 and 1 studies, so they were not considered in subgroups meta-analysis. Despite the differences in composition, Carisolv is a sodium-hypochlorite-based (NaOCl) agent while Papacarie is a papain enzyme-based agent; both agents did not interfere with bonding to dentin. Besides, after chemomechanical caries removal, the etching strategy - etch-and-rinse or self-etch also did not impact bond strength values. Although it might be thought that chemomechanical treated dentin could be a challenge for self-etch adhesive systems, this was not confirmed. The etch-and-rinse system Single Bond (3M Oral Care) was the most evaluated adhesive among the twenty adhesive systems used in the included studies.

In the present review, all included studies considered human teeth with natural or induced dentin caries by in situ models<sup>18</sup>, or pH cycling.<sup>22,23</sup> Even though artificial caries induction promotes easier standardized dentin surface, only these three studies considered laboratory protocol. Although some changes in carious dentin may occur in extracted teeth, teeth with natural lesions are closer to the clinical situation. Despite laboratory studies often considered sound dentin as a substrate for bonding, the present systematic review only considered studies that evaluated the bond strength to carious dentin subjected to chemomechanical and conventional caries removal.

Five studies considered natural carious dentin from primary teeth.<sup>12,28,32,38,39</sup> For primary dentin, however, chemomechanical caries removal negatively affected bond strength values compared to conventional methods. Primary dentin is less mineralized<sup>44</sup> and more permeable due to higher tubular density,<sup>44,45</sup> and these characteristics are usually associated with lower bond strength values observed in primary compared to permanent teeth.<sup>46</sup> Similarly, the effect of chemomechanical agents in less mineralized primary dentin could be pointed as a reason for the findings of this systematic review.

Conventional caries removal was conducted using carbide or diamond burs in high-speed, round burs in slow-speed, and hand excavators. The endpoint for caries removal, in most studies, was based on visual and tactile inspection. Some included studies also used laser fluorescence as dentin removal endpoint, and in only two studies, caries detection solution was used.<sup>17,25</sup> For chemomechanical agents, caries removal was repeated until the gel became clear. The information on whether the total or selective dentin caries removal was not described in most included studies.

Most studies used the microtensile bond strength test to assess the outcome bond strength test, which is considered a versatile and standard bond strength testing method.<sup>48</sup> Nevertheless, the shear bond strength test was used in three studies<sup>23,28,35</sup> and tensile test in one

of the included studies.<sup>32</sup> Despite this, and the fact that only human teeth were used, significant heterogeneity was found for the overall and sub-groups meta-analysis, as commonly found in the meta-analysis of laboratory studies.<sup>46,48,49</sup> For this reason, the random effect model was used in meta-analysis. Furthermore, most studies presented a moderate risk of bias, with several undescribed or unclear parameters considered in the risk of bias. Therefore, the results of this review should be interpreted with caution, on account of heterogeneity and the risk of bias of the included studies. Nevertheless, the search in four databases probably provide the records of laboratory studies on chemomechanical caries removal on bonding. Studies from several research groups identified by the first author country, languages, and publication year are included. Data from gray literature was usually incomplete and thus was not included in this systematic review. Even so, high-quality laboratory studies are still needed to substantiate the obtained results. Furthermore, despite their limitations, considering laboratory studies as helpful to predict the influence of substrate conditions on bonding,<sup>50</sup> the results of this systematic review showed that chemomechanical caries removal did not influence bonding of adhesive systems to dentin, except when primary dentin is considered.

## **5. CONCLUSION**

The evidence from laboratory studies supports the chemomechanical caries removal did not influence the adhesive systems bond strength to dentin. Chemomechanical agents can impair the bonding to primary dentin.

### **Why this paper is important to pediatric dentists**

Chemomechanical caries removal can be used in clinical practice with no detrimental effect on the bonding of adhesive systems.

In primary teeth, it is essential to consider the advantages of using chemomechanical agents, as they can jeopardize the bonding of adhesive systems to dentin.





## Figure legends

Figure 1. Flow diagram for studies 'search and inclusion according to PRISMA 2020.

Figure 2. Overall meta-analysis comparing conventional *vs* chemomechanical caries removal on bond strength values.

Figure 3. Forest plot for bond strength values comparing conventional *vs* chemomechanical caries removal by agent.

Figure 4. Forest plot for bond strength values comparing conventional *vs* chemomechanical caries removal by adhesive systems 'etching strategy.

Figure5. Forest plot for bond strength values comparing conventional *vs* chemomechanical caries removal on primary teeth.

## REFERENCES

1. Emara R, Krois J, Schwendicke F. *Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping*. J Dent. 2020;96:103330.
2. Schwendicke F, Dörfer CE, Paris S. *Incomplete caries removal: a systematic review and meta-analysis*. J Dent Res. 2013;92:306-314.
3. Banerjee A, Kidd EA, Watson TF. *In vitro validation of carious dentin removed using different excavation criteria*. Am J Dent. 2003;16:228-230.
4. Douglas C, Ana F, Franciele O, Eloisa B, Bruno C. *Effect of Carisolv and Papacarie on the resin dentin bond strength in sound and caries affected primary molars*. Braz J Oral Sci. 2010;9:25–29.
5. Ericson D, Zimmerman M, Raber H, Götrick B, Bornstein R, Thorell J. *Clinical evaluation of efficacy and safety of a new method for chemo-mechanical removal of caries. A multi-centre study*. Caries Res. 1999;33:171-177.
6. Fure S, Lingström P. *Evaluation of the chemomechanical removal of dentine caries in vivo with a new modified Carisolv gel*. Clin Oral Investig. 2004;8(3):139-144.
7. Schwendicke F. *Caries removal in primary teeth using Papacarie*. Evid Based Dent. 2018;19(3):74.
8. Hosein T, Hasan A. *Efficacy of chemo-mechanical caries removal with Carisolv*. J Coll Physicians Surg Pak. 2008;18:222-225.
9. Hossain M, Nakamura Y, Tamaki Y, Yamada Y, Jayawardena JA, Matsumoto K. *Dentinal composition and Knoop hardness measurements of cavity floor following carious dentin removal with Carisolv*. Oper Dent. 2003;28:346-351.
10. Schwendicke F, Paris S, Tu YK. *Effects of using different criteria for caries removal: a systematic review and network meta-analysis*. J Dent. 2015;43:1-15.

11. Cebe MA, Ozturk B, Karaarslan ES. *Effect of caries removal techniques on bond strength to caries affected dentin on gingival wall: AFM observation of dentinal surface.* J Adhes Sci Technol 2016;30:157-170.
12. Faustino-Silva DD, Leitune VCB, Collares FM, Figueiredo MC, Samuel SMW. *Resistência de união do adesivo à dentina de dentes decíduos submetidos a dois métodos de remoção químico-mecânica da cárie.* Rev Faculd Odontol. 2009;14:234-238.
13. Sirin Karaarslan E, Yildiz E, Cebe MA, Yegin Z, Ozturk B. *Evaluation of micro-tensile bond strength of caries-affected human dentine after three different caries removal techniques.* J Dent. 2012;40:793-801.
14. El-Kholany NR, Abdelaziz KM, Zaghoul NM, Aboulenien N. *Bonding of single-component adhesives to dentin following chemomechanical caries removal.* J Adhes Dent. 2005;7:281-287.
15. Naik SV, Shashikiran ND, Chaitra NL, Syed G. *A microtensile bond strength evaluation of a single-bottle adhesive to caries-affected dentin in conventional versus minimal invasive caries removal techniques: An in-vitro study.* Indian J Dent. 2014;5:127-131.
16. Neves Ade A, Coutinho E, Cardoso MV, de Munck J, Van Meerbeek B. *Micro-tensile bond strength and interfacial characterization of an adhesive bonded to dentin prepared by contemporary caries-excavation techniques.* Dent Mater. 2011;27:552-562.
17. Hamama HH, Yiu CK, Burrow MF. *Effect of chemomechanical caries removal on bonding of self-etching adhesives to caries-affected dentin.* J Adhes Dent. 2014;16:507-516.
18. Botelho Amaral FL, Martão Florio F, Bovi Ambrosano GM, Basting RT. *Morphology and microtensile bond strength of adhesive systems to in situ-formed caries-affected dentin after the use of a papain-based chemomechanical gel method.* Am J Dent. 2011;24:13-19.

19. Higgins J, Green S, editors. *Cochrane handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available from [www.cochranehandbook.org](http://www.cochranehandbook.org)
20. Liberati A, Altman DG, Tetzlaff J, et al. *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration*. PLoS Med 2009;6:e1000100.
21. Sarkis-Onofre R, Skupien JA, Cenci MS, Moraes RR, Pereira-Cenci T. *The role of resin cement on bond strength of glass-fiber posts luted into root canals: a systematic review and meta-analysis of in vitro studies*. Oper Dent 2014;39:E31–E44.
22. Gianini RJ, do Amaral FL, Flório FM, Basting RT. *Microtensile bond strength of etch-and-rinse and self-etch adhesive systems to demineralized dentin after the use of a papain-based chemomechanical method*. Am J Dent. 2010;23:23-28.
23. Lopes MC, Mascarini RC, da Silva BM, Flório FM, Basting RT. *Effect of a papain-based gel for chemomechanical caries removal on dentin shear bond strength*. J Dent Child. 2007;74:93-97.
24. Piva E, Ogliari FA, Moraes RR, Corá F, Henn S, Correr-Sobrinho L. *Papain-based gel for biochemical caries removal: influence on microtensile bond strength to dentin*. Braz Oral Res. 2008;22:364-370.
25. Tachibana A, Marques MM, Soler JM, Matos AB. *Erbium, chromium:yttrium scandium gallium garnet laser for caries removal: influence on bonding of a self-etching adhesive system*. Lasers Med Sci. 2008;23:435-441.
26. Aggarwal V, Singla M, Yadav S, Yadav H. *The effect of caries excavation methods on the bond strength of etch-and-rinse and self-etch adhesives to caries affected dentine*. Aust Dent J. 2013;58:454-460.

27. Chittem J, Sajjan GS, Varma KM. *Comparative evaluation of microshear bond strength of the caries-affected dentinal surface treated with conventional method and chemomechanical method (papain)*. J Conserv Dent. 2015;18:369-373.
28. Maru VP, Shakuntala BS, Dharma N. *Evaluation of Marginal Leakage and Shear Bond Strength of Bonded Restorations in Primary Teeth after Caries Removal by Conventional and Chemomechanical Techniques*. Int Sch Res Notices. 2014;2014:854816.
29. Nair S, Nadig R, S Pai V, Gowda Y. *Effect of Papain-based chemomechanical agent on structure of dentin and bond strength: An in vitro study*. Int J Clin Pediatr Dent. 2018;11:161-166.
30. Cehreli ZC, Yazici AR, Akca T, Ozgünaltay G. *A morphological and micro-tensile bond strength evaluation of a single-bottle adhesive to caries-affected human dentine after four different caries removal techniques*. J Dent. 2003;31:429-435.
31. Yildiz E, Sirinkaraarslan E, Yegin Z, Cebe MA, Tosun G. *Effect of caries removal techniques on the bond strength of adhesives to caries-affected primary dentin in vitro*. Eur J Paediatr Dent. 2013;14:209-214.
32. Olivares Espinoza JA, Sáenz Pasco GN. *Fuerzas de adhesión de un sistema adhesivo de quinta generación en superficies dentarias tratadas con agentes químico-mecánicos*. Odontol Pediatr 2013;12:6-13.
33. Ucar E, Ramírez R, Orellana N, Setien V. *Influencia del método de remoción de caries en la fuerza de adhesión a dentina afectada*. Acta Odontol Venez. 2013;51:1.
34. Banerjee A, Kellow S, Mannocci F, Cook RJ, Watson TF. *An in vitro evaluation of microtensile bond strengths of two adhesive bonding agents to residual dentine after caries removal using three excavation techniques*. J Dent. 2010;38:480-489.
35. Haak R, Wicht MJ, Noack MJ. *Does chemomechanical caries removal affect dentine adhesion?* Eur J Oral Sci. 2000;108:449-455.

36. Li H, Wang WM, Yu SL, Wen Q. *Morphological and microtensile bond strength evaluation of three adhesive systems to caries-affected human dentine with chemomechanical caries removal*. J Dent. 2011;39:332-339.
37. Sonoda H, Banerjee A, Sherriff M, Tagami J, Watson TF. *An in vitro investigation of microtensile bond strengths of two dentine adhesives to caries-affected dentine*. J Dent. 2005;33:335-342.
38. Zawaideh F, Palamara JE, Messer LB. *Bonding of resin composite to caries-affected dentin after Carisolv(®) treatment*. Pediatr Dent. 2011;33(3):213-220.
39. Wahby MAR, ElMasry ES, El Sheikh MA, Youness SB. *In vitro Study Evaluating the Micro-Tensile Bond Strength of Different Restorative Materials After Treatment by Chemo-Mechanical*. Agent Nat Sci 2014;12:22-26
40. Cardoso M, Coelho A, Lima R, Amaro I, Paula A, Marto CM, Sousa J, Spagnuolo G, Marques Ferreira M, Carrilho E. *Efficacy and Patient's Acceptance of Alternative Methods for Caries Removal-a Systematic Review*. J Clin Med. 2020;9:3407.
41. Perdigão J. *Dentin bonding – variables related to the clinical situation and the substrate treatment*. Dent Mater. 2010;26:e24–e37.
42. Corrêa FN, Rodrigues Filho LE, Rodrigues CR. *Evaluation of residual dentin after conventional and chemomechanical caries removal using SEM*. J Clin Pediatr Dent. 2008;32:115-120.
43. Angker L, Nockolds C, Swain MV, Kilpatrick N. *Quantitative analysis of the mineral content of sound and carious primary dentine using BSE imaging*. Arch Oral Biol. 2004;49:99-107.
44. Lenzi TL, Guglielmi Cde A, Arana-Chavez VE, Raggio DP. *Tubule density and diameter in coronal dentin from primary and permanent human teeth*. Microsc Microanal 2013;19:1445-1449.

45. Sumikawa DA, Marshall GW, Gee L, Marshall SJ. *Microstructure of primary tooth dentin*. *Pediatr Dent*. 1999;21:439-444.
46. Pires CW, Soldera EB, Bonzanini LIL, Lenzi TL, Soares FZM, Montagner AF, Rocha RO. *Is Adhesive Bond Strength Similar in Primary and Permanent Teeth? A Systematic Review and Meta-analysis*. *J Adhes Dent*. 2018;20:87-97.
47. Sano H, Chowdhury AFMA, Saikaew P, Matsumoto M, Hoshika S, Yamauti M. *The microtensile bond strength test: Its historical background and application to bond testing*. *Jpn Dent Sci Rev*. 2020;56:24-31.
48. Cuevas-Suárez CE, da Rosa WLO, Lund RG, da Silva AF, Piva E. *Bonding Performance of Universal Adhesives: An Updated Systematic Review and Meta-Analysis*. *J Adhes Dent*. 2019;21:7-26.
49. Montagner AF, Sarkis-Onofre R, Pereira-Cenci T, Cenci MS. *MMP Inhibitors on Dentin Stability: A Systematic Review and Meta-analysis*. *J Dent Res*. 2014;93:733-43.
50. Shono Y, Ogawa T, Terashita M, Carvalho RM, Pashley EL, Pashley DH. *Regional measurement of resin–dentin bonding as an array*. *J Dent Res* 1999;78:699–705.

Table 1. Descriptive data of included studies

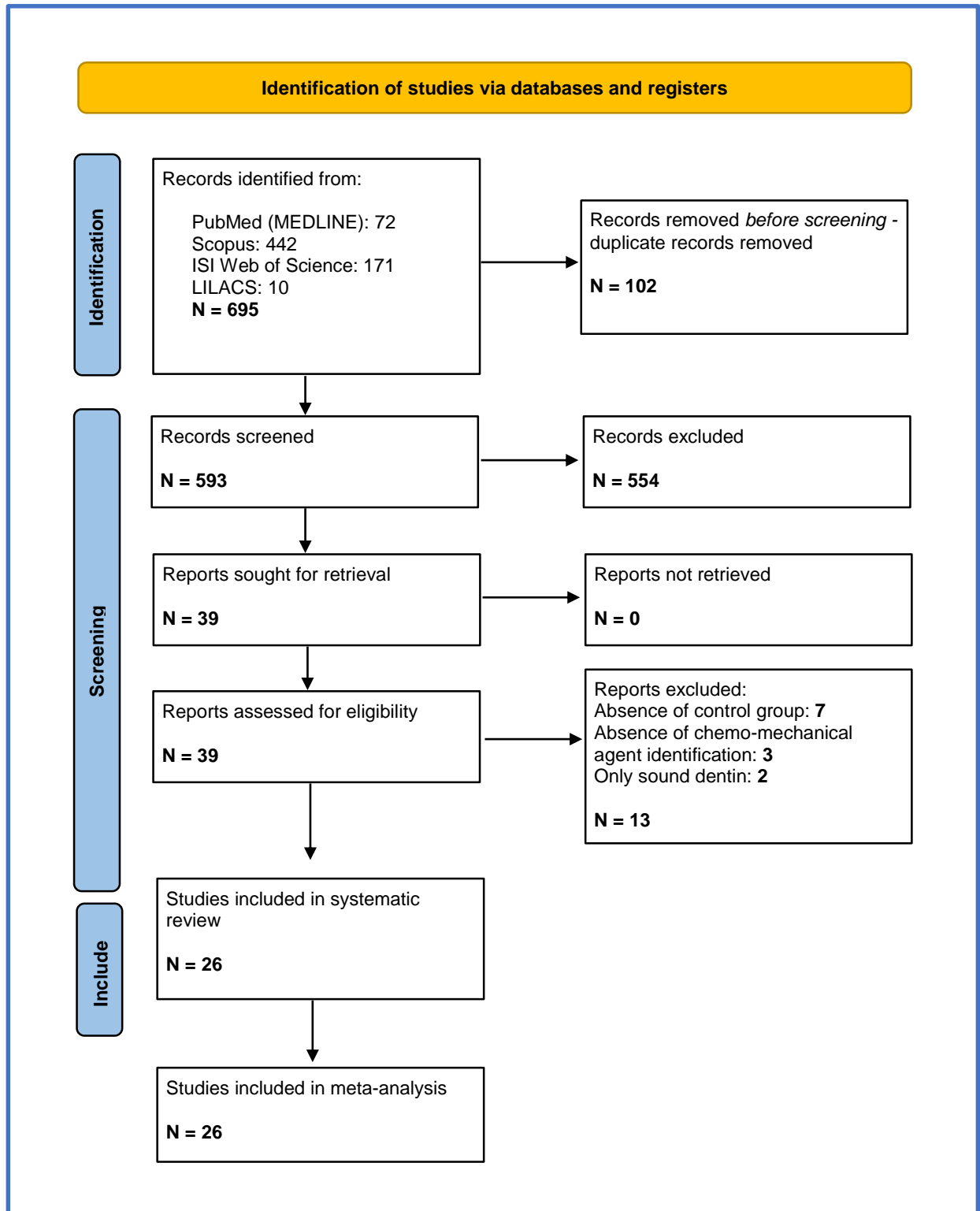
Author	Country	Language	Substrate	Specimens per group	Dentin condition	Chemo-mechanical agent	Control caries removal	Adhesive system*	Composite resin*	Bond strength test
Aggarwal et al., 2013	India	English	Human permanent molars	10 sections	Natural caries	Carisolv® gel	Tungsten carbide bur	Single Bond One Coat Self Etching Bond Adper Easy Bond	Z350 Synergy D6 Universal	Microtensile bond strength
Banerjee et al. 2010	UK	English	Human permanent molars	7 teeth	Natural caries	Carisolv™ gel SFC-V (Biosolv)	Spoon-shaped hand excavator	Adper Scotchbond 1XT Filtek Silorane adhesive	Filtek Supreme Filtek Silorane	Microtensile bond strength
Botelho Amaral et al., 2011	Brazil	English	Human permanent molars	14 slabs	In situ caries induction	Papacarie	Curette	Adper Single Bond 2 Clearfil SE Bond Clearfil Tri S Bond	Filtek Z250	Microtensile bond strength
Cebe et al., 2016	Turkey	English	Human permanent molars	5 teeth	Natural caries	Carisolv® gel Multimix	Round steel bur	Adper SE Plus Clearfil S3 bond	Filtek Z 250 Clearfil AP-X	Microtensile bond strength
Cehreli et al., 2003	Turkey	English	Human permanent molars	6 teeth	Natural caries	Carisolv™ gel	Round bur	Single Bond	Filtek P60	Microtensile bond strength

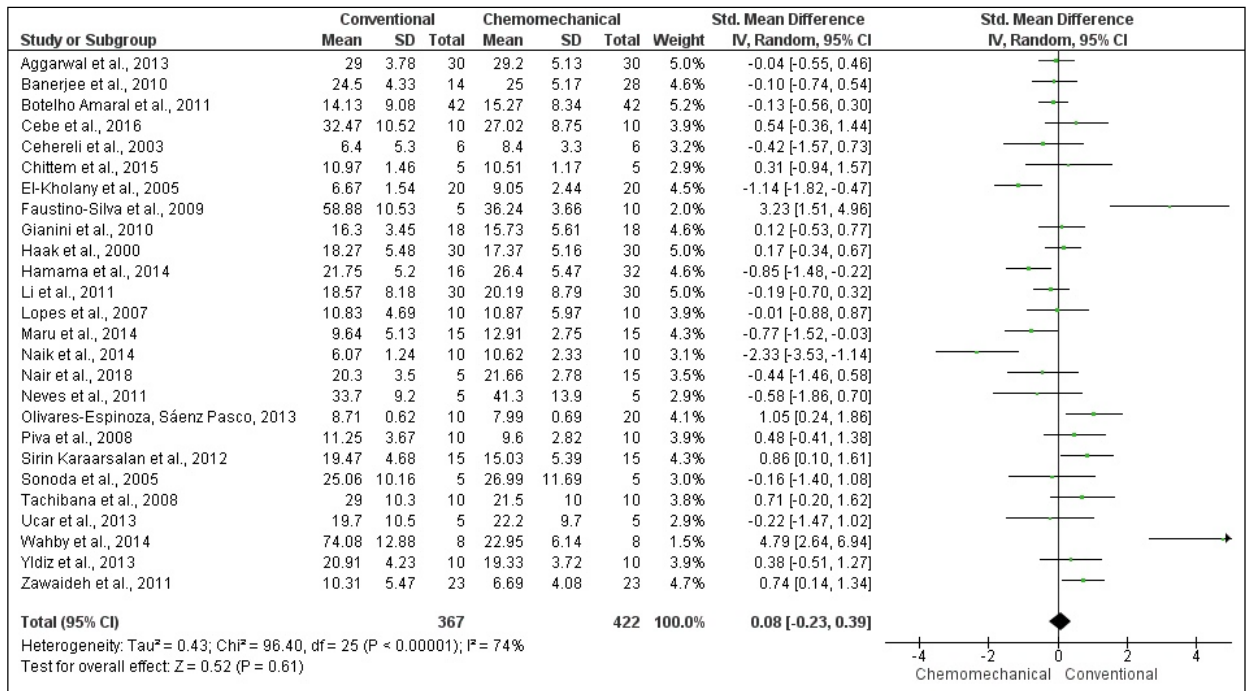


Chittem et al., 2015	India	English	Human permanent molars	5 teeth	Natural caries	Carie-care	round steel bur	Single Bond	Filtek Z 350	Microshear bond strength
El-Kholany et al., 2005	Egypt	English	Human permanent molars	10 teeth	Natural caries	Carisolv® gel	Diamond bur	Syntac Single Component Excite	Tetric Ceram	Microtensile bond strength
Faustino-Silva et al., 2009	Brazil	Portuguese	Human primary molars	5 teeth	Natural caries	Carisolv® gel Papacarie	Round steel bur	Single Bond	Z 100	Microtensile bond strength
Gianini et al., 2010	Brazil	English	Human permanent molars	6 slabs	Artificial caries induction (pH cycling)	Papacarie	Mechanical excavators - curette	SingleBond AdheSE Adper Prompt	Filtek Z 250	Microtensile bond strength
Haak et al., 2000	Germany	English	Human permanent molars	10 teeth	Natural caries	Carisolv™ gel	Round bur	Prime & Bond NT Syntac SC Etch & Prime 3.0	Dyract AP Tetric Ceram Definite	Shear bond strength
Hamama et al., 2104	Egypt	English	Human permanent molars	8 teeth	Natural caries	Carisolv®gel Multimix Papacarie	Round steel bur	Clearfil SE Bond Clearfil S3	Filtek Z 250	Microtensile bond strength
Li et al., 2011	China	English	Human permanent molars	5 teeth	Natural caries	Carisolv™ gel	Bur	Prime & Bond NT One Step Adper Prompt-L-Pop	Dyract AP Renew Z100	Microtensile bond strength
Lopes et al., 2007	Brazil	English	Human permanent molars	10 slabs	Artificial caries induction (pH cycling)	Papacarie	Curette	Single Bond	Filtek Z 100	Shear bond strength
Maru et al., 2014	India	English	Human primary molars	15 teeth	Natural caries	Papacarie	Carbide bur	Adper Ease One	Z 250	Shear bond strength <sup>§</sup>
Naik et al., 2014	India	English	Human permanent molars	10 teeth	Natural caries	Carisolv™ gel	Round carbide bur	Adper Ease One	Filtek Z 350	Microtensile bond strength
Nair et al., 2018	India	English	Human permanent molars	5 teeth	Natural caries	Carisolv®gel Multimix Papacarie Carie-care	Tungsten carbide bur	Single Bond	Filtek Z 350	Microtensile bond strength
Neves et al., 2011	Brazil	English	Human permanent molars	7 teeth	Natural caries	Carisolv™ gel	Tungsten-carbide round bur	Clearfil SE Bond	Filtek Z 100	Microtensile bond strength
Olivares Espinoza, Sáenz Pasco, 2013	Peru	Spanish	Human primary molars	10 teeth	Natural caries	Carisolv® gel Papacarie	Diamond bur	Single Bond	Z 250	Tensile bond strength
Piva et al., 2008	Brazil	English	Human permanent molars	5 teeth	Natural caries	Papacarie	Tungsten carbide bur	Clearfil SE Bond Prime & Bond NT	Charisma	Microtensile bond strength
Sirin Karaarslan et al., 2012	Turkey	English	Human permanent molars	5 teeth	Natural caries	Carisolv® gel Multimix	Round steel bur	Adper Single Bond 2 G Bond Clearfil SE Bond	Filtek Z 250 Gradia Direct Clearfil Photo Posterior	Microtensile bond strength
Sonoda et al., 2005	Japan	English	Human permanent molars	5 teeth	Natural caries	Carisolv™ gel	Spoon excavator	Prime & Bond NT	Esthet.X	Microtensile bond strength
Tachibana et al., 2008	Brazil	English	Human permanent molars	10 teeth	Natural caries	Carisolv™ gel	Round steel bur	Clearfil SE Bond	Astralis 3	Microtensile bond strength
Yildiz et al., 2013	Turkey	English	Human permanent molars	5 teeth	Natural caries	Carisolv® gel Multimix	Round steel bur	Adper Single Bond 2 G Bond	Z 250	Microtensile bond strength
Zawaideh et al., 2011	Jordan	English	Human primary molars	23 specimens	Natural caries	Carisolv® gel	Round steel bur	Single Bond	Filtek Supreme Universal	Microshear bond strength
Ucar et al., 2013	Venezuela	Spanish	Human permanent molars	5 teeth	Natural caries	Papacarie	Round carbide bur	Excite	Brilliant Enamel New Line	Microtensile bond strength
Wahby et al., 2014	Egypt	English	Human primary molars	8 teeth	Natural caries	Papacarie	Round bur	#	Herculite XRV	Microtensile bond strength
<sup>§</sup> Only described as a two-step etch-and-rinse adhesive system <sup>§</sup> Thermocycled										

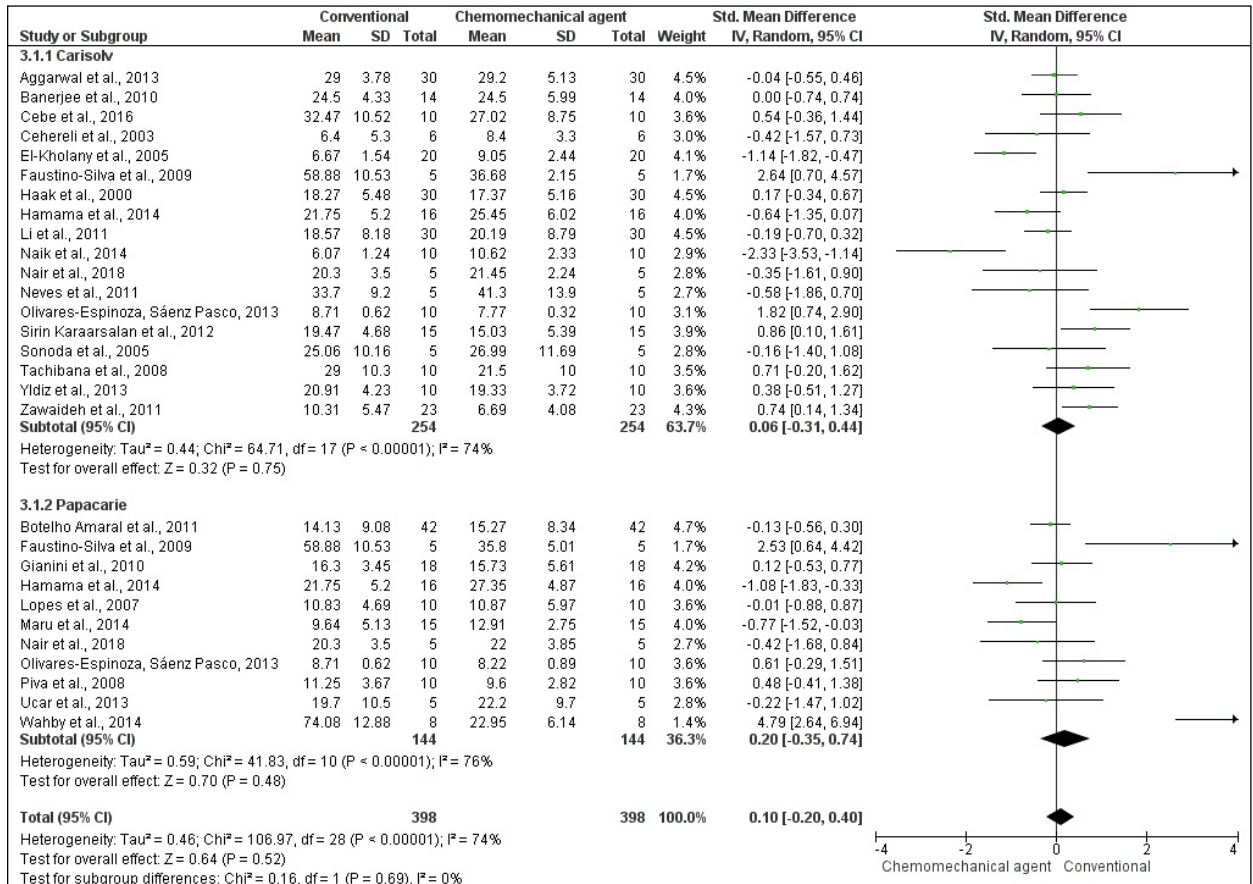
Table 2. Risk of bias

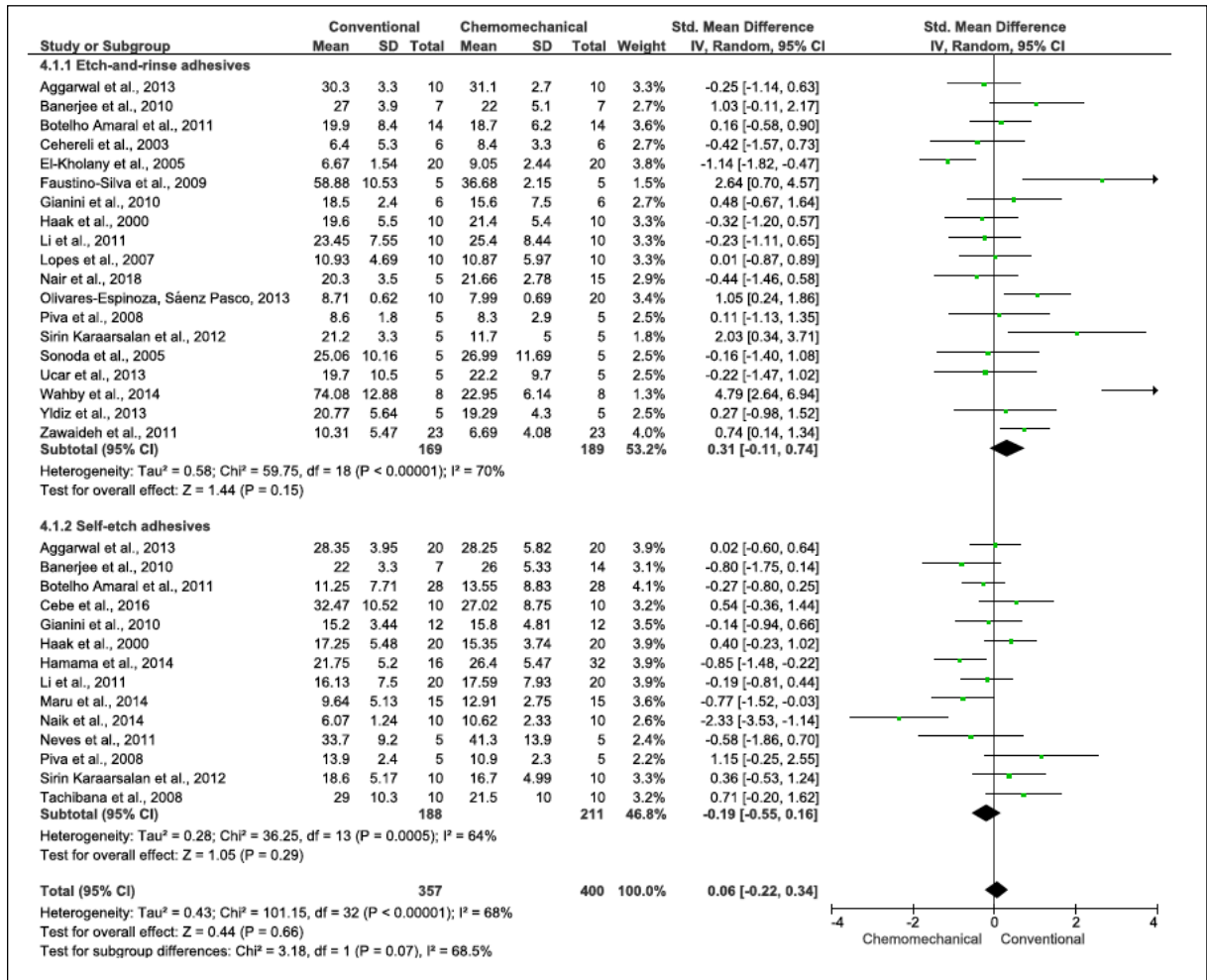
Author	Sample size calculation	Random sequence	Same number of teeth per group	Single operator	Manufacturers' instructions
Aggarwal et al., 2013 <sup>26</sup>	N	N	Y	N	N
Banerjee et al. 2010 <sup>34</sup>	N	Y	Y	Y	Y
Botelho Amaral et al., 2011 <sup>18</sup>	N	Y	Y	N	Y
Cebe et al., 2016 <sup>11</sup>	N	Y	Y	N	Y
Cehreli et al., 2003 <sup>30</sup>	N	Y	Y	N	Y
Chittem et al., 2015 <sup>27</sup>	N	Y	Y	N	Y
El-Kholany et al., 2005 <sup>14</sup>	N	N	Y	N	Y
Faustino-Silva et al., 2009 <sup>12</sup>	Y	N	Y	N	N
Gianini et al., 2010 <sup>22</sup>	N	Y	Y	N	Y
Haak et al., 2000 <sup>35</sup>	N	Y	Y	N	N
Hamama et al., 2104 <sup>17</sup>	N	Y	Y	N	Y
Li et al., 2011 <sup>36</sup>	N	Y	Y	N	Y
Lopes et al., 2007 <sup>23</sup>	N	Y	Y	N	Y
Maru et al., 2014 <sup>28</sup>	N	Y	N	N	N
Naik et al., 2014 <sup>15</sup>	N	Y	Y	N	N
Nair et al., 2018 <sup>29</sup>	N	Y	Y	N	Y
Neves et al., 2011 <sup>16</sup>	N	N	Y	N	Y
Olivares Espinoza, Sáenz Pasco, 2013 <sup>32</sup>	N	N	Y	N	N
Piva et al., 2008 <sup>24</sup>	N	Y	Y	N	Y
Sirin Karaarslan et al., 2012 <sup>13</sup>	N	Y	Y	N	Y
Sonoda et al., 2005 <sup>37</sup>	N	Y	Y	Y	Y
Tachibana et al., 2008 <sup>25</sup>	N	Y	Y	N	N
Yildiz et al., 2013 <sup>31</sup>	N	Y	Y	N	Y
Zawaideh et al., 2011 <sup>38</sup>	N	Y	Y	N	N
Ucar et al., 2013 <sup>33</sup>	N	N	Y	N	N
Wahby et al., 2014 <sup>39</sup>	N	N	Y	N	Y

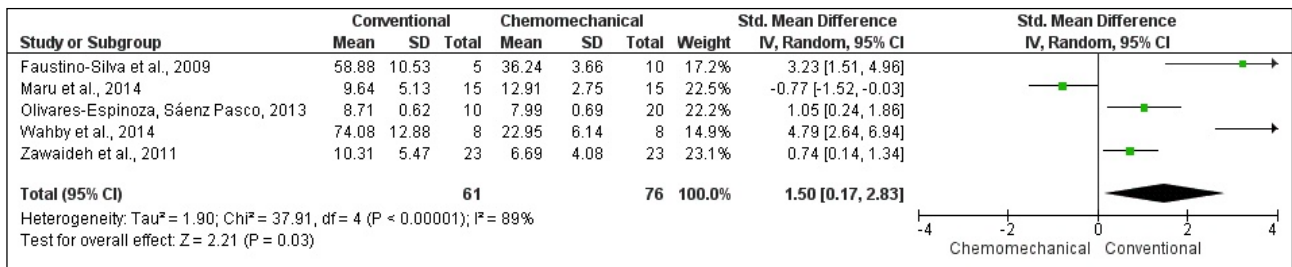














### **3 CONCLUSÃO**

Por meio da revisão sistemática e meta-análise realizada pode-se concluir que a remoção químico-mecânica de tecido cariado não impacta na resistência de união de sistemas adesivos, exceto em dentina de dentes decíduos, prejudicando a adesão à esse substrato.

Sugere-se assim, que o possível efeito negativo do emprego de agentes de remoção químico-mecânica seja considerado quando do uso em dentes decíduos.

## REFERÊNCIAS

- BANERJEE A, KIDD EA, WATSON TF. In vitro validation of carious dentin removed using different excavation criteria. **Am J Dent.** 2003;16:228-230
- BOTELHO AMARAL FL, MARTÃO FLORIO F, BOVI AMBROSANO GM, BASTING RT. Morphology and microtensile bond strength of adhesive systems to in situ-formed caries-affected dentin after the use of a papain-based chemomechanical gel method. **Am J Dent.** 2011;24:13-19.
- CEBE MA, OZTURK B, KARAARSLAN ES. Effect of caries removal techniques on Bond strength to caries affected dentin on gingival wall: AFM observation of dentinal surface. **J Adhes Sci Technol** 2016;30:157-170.
- EL-KHOLANY NR, ABDELAZIZ KM, ZAGHLOUL NM, ABOULENIEN N. Bonding of single-component adhesives to dentin following chemomechanical caries removal. **J Adhes Dent.** 2005;7:281-287.
- EMARA R, KROIS J, SCHWENDICKE F. Maintaining pulpal vitality: Cost-effectiveness analysis on carious tissue removal and direct pulp capping. **J Dent.** 2020;96:103330.
- ERICSON D, ZIMMERMAN M, RABER H, GÖTRICK B, BORNSTEIN R, THORELL J. Clinical evaluation of efficacy and safety of a new method for chemo-mechanical removal of caries. A multi-centre study. **Caries Res.** 1999;33:171-177.
- FAUSTINO-SILVA DD, LEITUNE VCB, COLLARES FM, FIGUEIREDO MC, SAMUEL SMW. Resistência de união do adesivo à dentina de dentes decíduos submetidos a dois métodos de remoção químico-mecânica da cárie. **Rev Faculd Odontol.** 2009;14:234-238.
- FURE S, LINGSTRÖM P. Evaluation of the chemomechanical removal of dentine caries in vivo with a new modified Carisolv gel. **Clin Oral Investig.** 2004;8(3):139-144.
- HAMAMA HH, YIU CK, BURROW MF. Effect of chemomechanical caries removal on bonding of self-etching adhesives to caries-affected dentin. **J Adhes Dent.** 2014;16:507-516.
- HOSSAIN M, NAKAMURA Y, TAMAKI Y, YAMADA Y, JAYAWARDENA JA, MATSUMOTO K. Dentinal composition and Knoop hardness measurements of cavity floor following carious dentin removal with Carisolv. **Oper Dent.** 2003;28:346-351.
- NAIK SV, SHASHIKIRAN ND, CHAITRA NL, SYED G. A microtensile bond strength evaluation of a single-bottle adhesive to caries-affected dentin in conventional versus minimal invasive caries removal techniques: An in-vitro study. **Indian J Dent.** 2014;5:127-131.
- NEVES A DE A, COUTINHO E, CARDOSO MV, DE MUNCK J, VAN MEERBEEK B. Micro-tensile bond strength and interfacial characterization of an adhesive bonded to dentin prepared by contemporary caries-excitation techniques. **Dent Mater.** 2011;27:552-562.

SCHWENDICKE F, DÖRFER CE, PARIS S. Incomplete caries removal: a systematic review and meta-analysis. **J Dent Res.** 2013;92:306-314 (EMARA; KROIS; SCHWENDICKE, 2020; SCHWENDICK; DÖRFER; PARIS, 2013).

## ANEXO 1

### INTERNATIONAL JOURNAL OF PAEDIATRIC DENTISTRY

#### Author Guidelines

##### Sections

- 1. Submission**
- 2. Aims and Scope**
- 3. Manuscript Categories and Requirements**
- 4. Preparing the Submission**
- 5. Editorial Policies and Ethical Considerations**
- 6. Author Licensing**
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#### 1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

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*International Journal of Paediatric Dentistry* publishes papers on all aspects of paediatric dentistry including: growth and development, behaviour management, diagnosis, prevention, restorative treatment and issue relating to medically compromised children or those with disabilities. This peer-reviewed journal features scientific articles, reviews, case reports, short communications and abstracts of current paediatric dental research. Analytical studies with a scientific novelty value are preferred to descriptive studies. Case reports illustrating unusual conditions and clinically relevant observations are acceptable but must be of sufficiently high quality to be considered for publication; particularly the illustrative material must be of the highest quality.

#### 3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

##### i. Original Articles

Divided into: Summary, Introduction, Material and methods, Results, Discussion, Bullet points, Acknowledgements, References, Figure legends, Tables and Figures arranged in this order.

- **Summary** should be structured using the following subheadings: Background, Hypothesis or Aim, Design, Results, and Conclusions and should be less than 200 words.
- **Introduction** should be brief and end with a statement of the aim of the study or hypotheses tested. Describe and cite only the most relevant earlier studies. Avoid presentation of an extensive review of the field.
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- **Discussion** section presents the interpretation of the findings. This is the only proper section for subjective comments and reference to previous literature. Avoid repetition of results, do not use subheadings or reference to tables in the results section.
- **Bullet Points:** Authors will need to provide no more than 3 'key points' that summarise the key messages of their paper to be published with their article. The key points should be written with a practitioner audience in mind under the heading:
  - \*Why this paper is important to paediatric dentists.

References: Maximum 30.

## ii. Review Articles

May be invited by the Editor.

## iii. Systematic reviews

We consider publishing systematic reviews if the manuscript has comprehensive and unbiased sampling of literature and covering topics related to Paediatric Dentistry.

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Articles for the *International Journal of Paediatric Dentistry* should include: a) description of search strategy of relevant literature (search terms and databases), b) inclusion criteria (language, type of studies i.e. randomized controlled trial or other, duration of studies and chosen endpoints, c) evaluation of papers and level of evidence. For examples see:

Twetman S, Axelsson S, Dahlgren H et al. Caries-preventive effect of fluoride toothpaste: a systematic review. *Acta Odontologica Scandinavica* 2003; 61: 347-355.

Paulsson L, Bondemark L, Söderfeldt B. A systematic review of the consequences of premature birth on palatal morphology, dental occlusion, tooth-crown dimensions, and tooth maturity and eruption. *Angle Orthodontist* 2004; 74: 269-279.

## iv. Short Communications

Brief scientific articles or short case reports may be submitted, which should be no longer than three pages of double-spaced text and include a maximum of three illustrations. They should contain important, new, definitive information of sufficient significance to warrant publication. They should not be divided into different parts and summaries are not required.

References: Maximum 30.

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Short papers not exceeding 800 words, including a maximum of three illustrations and five references may be accepted for publication if they serve to promote communication between clinicians and researchers. If the paper describes a genetic disorder, the OMIM unique six-digit number should be provided for online cross reference (Online Mendelian Inheritance in Man).

A paper submitted as a Brief Clinical/Case Report should include the following:

- a short **Introduction** (avoid lengthy reviews of literature);
- the **Case report** itself (a brief description of the patient/s, presenting condition, any special investigations and outcomes);
- a **Discussion** which should highlight specific aspects of the case(s), explain/interpret the main findings and provide a scientific appraisal of any previously reported work in the field.

- **Bullet Points:** Authors will need to provide no more than 3 ‘key points’ that summarise the key messages of their paper to be published with their article. The key points should be written with a practitioner audience in mind under the heading:
- \*Why this paper is important to paediatric dentists.

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The title page should contain:

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Author contributions: A.S. and K.J. conceived the ideas; K.J. and R.L.M. collected the data; R.L.M. and P.A.K. analysed the data; and A.S. and K.J. led the writing;

iv. The author’s institutional affiliations where the work was conducted, with a footnote for the author’s present address if different from where the work was conducted;

v. Acknowledgments;

vi. Word count (excluding tables)

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Please refer to the journal’s authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

#### **Acknowledgments**

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned.

Thanks to anonymous reviewers are not appropriate.

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As papers are double-blind peer reviewed the main text file should not include any information that might identify the authors.

The main text file should be presented in the following order:

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ii. Main text;

iii. References;

iv. Tables (each table complete with title and footnotes);

v. Figure legends;

vi. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

#### **Abstract**

Abstracts and keywords are required for some manuscript types. For details on manuscript types that require abstracts, please refer to the ‘Manuscript Types and Criteria’ section.

### Keywords

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All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should cite references in consecutive order using Arabic superscript numerals. For more information about AMA reference style please consult the [AMA Manual of Style](#)

Sample references follow:

#### *Journal article*

1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. *J Comp Neurol* 1998;390:537-551.

#### *Book*

2. Voet D, Voet JG. *Biochemistry*. New York: John Wiley & Sons; 1990. 1223 p.

#### *Internet document*

3. American Cancer Society. *Cancer Facts & Figures 2003*.  
<http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf> Accessed March 3, 2003

### Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and \*, \*\*, \*\*\* should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

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Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted.

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*Author Guidelines Updated 08 February 2021*

## ANEXO 2

## PRISMA CHECKLIST

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Page 11
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 11
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 12, 13
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 13
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 14,15
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 13, 14
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 14
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 14,15
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 15
Data items	10 a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 15, 16
	10 b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 15, 16
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 16
Synthesis methods	13 a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 16

Section and Topic	Item #	Checklist item	Location where item is reported
	13 b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 16
	13 c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 16
	13 d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 16
	13 e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 16
	13 f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 16
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 15, 16
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
<b>RESULTS</b>			
Study selection	16 a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 16, 17
	16 b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 16, 17
Study characteristics	17	Cite each included study and present its characteristics.	Page 18
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 18
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2 to 5 Page 18
Results of syntheses	20 a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figures 2 to 5 Page 18
	20 b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figures 2 to 5 Page 18
	20 c	Present results of all investigations of possible causes of heterogeneity among study results.	Figures 2 to 5 Page 18
	20 d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figures 2 to 5 Page 18

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
<b>DISCUSSION</b>			
Discussion	23 a	Provide a general interpretation of the results in the context of other evidence.	Pages 19, 20
	23 b	Discuss any limitations of the evidence included in the review.	Pages 20, 21
	23 c	Discuss any limitations of the review processes used.	Page 21
	23 d	Discuss implications of the results for practice, policy, and future research.	Page 21
<b>OTHER INFORMATION</b>			
Registration and protocol	24 a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24 b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24 c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-