REVIEW ARTICLE

# Evaluation of Casein Phosphopeptide–Amorphous Calcium Phosphate Effect on the Bond Strength of Self-etch Adhesives to Dentin: A Systematic Review

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## Abstract

Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) is used as a remineralizing agent, ultimately reducing dental caries. The systematic review was performed as a review on the evaluation of CPP–ACP effect on the bond strength of self-etch adhesives to dentin. Medline (via PubMed) and Google Scholar were among the databases that were searched. Articles written exclusively in English and released up until 30 November 2021, were included. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria were followed in the conduct of this research. There were 479 published studies found in the search results. Thirteen studies were chosen following full-text analysis and the elimination of duplicate studies. Overall, the outcomes showed that CPP–ACP has positive impacts on the bond strength of self-etch adhesive to dentin. The search keywords were "CPP–ACP (Title/Abstract)" OR "tooth mousse (Title/Abstract)" OR "MI-paste (Title/Abstract)" AND "bond strength (Title/Abstract)" OR "tensile bond strength (Title/Abstract)" OR "microtensile bond strength (Title/Abstract)" OR "shear bond strength (Title/Abstract)." The bond-strength test is used to determine the ability of self-etch adhesives to remain in contact with the application of CPP–ACP as a remineralizing agent on the dentin while under stress. The impact of CPP–ACP application on dentin's bond strength to self-etch adhesives cannot be concluded due to the significant degree of variation among the included research.

**Keywords:** Dental bonding, Dental etching, Systematic review.

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## Introduction

Dental caries is slowed down by a novel bioactive substance called casein phosphopeptide–amorphous calcium phosphate (CPP–ACP), which is generated from the milk protein casein. The sequence of clusters is "-Ser (P)-Ser (P)-Ser (P)." The main phosphoprotein in cow's milk, casein, makes for nearly 80% of its total protein content.[1] Furthermore, CPP–ACP's antibacterial and anticalculus properties can prevent demineralization, encourage remineralization of enamel, and postpone the formation of biofilms.[2] Also, CPP–ACP maintains the condition of supersaturation at the tooth structure by gradually raising the calcium phosphate content in plaque. As a result, it may serve as a calcium phosphate reservoir, buffering the activities of free calcium and phosphate ions.[3]

Caries can be treated non-invasively by topical CPP–ACP therapy. By preserving ionic phosphate and calcium supersaturation, it has been demonstrated to be useful in halting dentin caries by manipulating bioavailable calcium phosphate levels.[4] They can also block the dentinal tubules and reduce the sensitivity; in cases of erosion, it neutralizes acid challenges from internal and external acid sources, and the biomimetic mineralization of dentin is induced through apatite formation along and between the phosphorylated dentin collagen fibers.[5–7]

Dental adhesives are resin monomer solutions containing solvents, curing initiators, inhibitors or stabilizers, and, occasionally, inorganic fillers. Buonocore founded adhesive dentistry in 1955 after discovering the advantages of acid etching. The idea of a generation has changed in dental adhesives due to the complexity of bonding agents, which ranges from "no etch" to "total etch" (fourth and fifth generations) to "self-etch" (sixth, seventh, and eighth generation) systems.[8] Self-etch adhesive systems are thought to be simplified adhesive materials because they do not need a separate acid conditioning process or wet post-rinse management. They are also thought to be straightforward to use and attach chemically to the tooth structure.[9]

Since CPP–ACP is being used more often to treat caries, it is possible that CPP–ACP was applied to the dentin surface of cavities prior to the restoration being placed. It is crucial to look into whether this will have an impact on how well self-etch adhesives adhere to dentin. The purpose of this systematic study is to assess the impact of CPP–ACP on the dentin bond strength of self-etch adhesives.

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**Conflict of interest:** None

## Materials and Methods

The present study corresponded to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) criteria, as available at http://www.prisma-statement.org. The registration number for this systematic review on PROSPERO is CRD42021240001. Four examiners conducted an independent search, using the electronic databases Medline (via PubMed) and Google Scholar to find publications published up until November 2021 without any year restrictions. Only articles written in the English language were taken into consideration for the review. The search keywords were "CPP–ACP (Title/Abstract)" OR "tooth mousse (Title/Abstract)" OR "MI-paste (Title/Abstract)" AND "bond strength (Title/Abstract)" OR "tensile bond strength (Title/Abstract)" OR "microtensile bond strength (Title/Abstract)" OR "shear bond strength (Title/Abstract)." Two authors of this study independently selected the retrieved studies by examining the titles and abstracts. When it was unable to evaluate the research-based just on their titles and abstracts, the complete text was accessible. Reading whole texts and selecting studies for inclusion based on eligibility requirements using the PICOS approach constitute the second stage. Duplicate studies in the database search were taken into consideration only once, and disagreements on the inclusion of a study were resolved by consensus with a third author. The reason for the exclusion of these studies is articles related to the bond strength of enamel, orthodontic brackets and dentin of primary teeth; studies in which CPP–ACP was not used as an intervention agent; studies are excluded if there was no control group (CG) as before and after studies and studies showed the strength of etch-and-rinse adhesives, glass ionomer cement as measured following application of CPP–ACP. The inclusion and exclusion criteria are given in Table 1.

## Results

A total of 479 published papers were found in the databases at first as a consequence of the search; however, 58 studies were eliminated since they were duplicates. A total of 26 studies were then included after titles and abstracts from 421 suitable papers were analyzed. The studies' failure to meet the inclusion criteria was the primary cause of the papers' rejection. Following a thorough review, thirteen studies were eliminated. A total of 13 studies in all were chosen for the systematic review as a result. Figure 1 shows the search strategy and results for the selection of studies.

### Quality Assessment

A prior study by AlShwaimi E et al. served as the foundation for and model for the risk of bias (Table 2) evaluation.[10] The following parameters for the study's quality assessment were described in the evaluation:

- The existence of a comparative group.
- Allocate the groups at random.
- An explanation of the sample size calculation.
- Using teeth free of restorations or cavities.
- Utilizing the materials in accordance with the guidelines provided by the manufacturers.
- A study carried out by one operator.
- Quantity of the materials used.
- Blinding of the observer.

## Discussion

Demineralization of tooth surface due to caries which requires prolonged application of therapeutic agents to repair enamel. Oral therapeutic agents which applied periodically must have desirable properties such as "high substantivity" or long-term activity. Furthermore, CPP–ACP shows the highest oral substantivity and higher anticariogenic properties.[11] Moreover, CPP–ACP can expose collagen fibers and increase mineral content as it has a remineralizing ability which would also enhance dentin bond strength and durability when applied to caries-affected dentin (CAD).[12]

An assessment was conducted on the caliber of every included study. One need for this evaluation was random allocation, which aims toward ensuring that every lesion has an equal chance of getting any of the experimental studies. Every study that was included provided sufficient procedures for assigning participants at random. Performance bias is another factor in evaluating quality, and it should be prevented by appropriately blinding participants and personnel. Only one study had mentioned about the blinding of the operator of the testing machine.[13] Due to the nature of the interventions, it was not possible to blind participants or the primary investigator to the interventions, as no other study had addressed the topic of participant or investigator blinding. Since both the participants and the operators were aware of the experimental technique, the risk of performance bias was deemed to be medium. The evaluation was predicated on the explanation of the following parameters for the quality assessment of the study: The use of teeth free of caries or restorations, the quantity of materials used, the number of materials used, the presence of a comparison group, random group assignment, the description of sample size calculation, study conducted by a single operator, and the blinding of the observer operating the machine.

Out of the 13 studies included, two studies (15.4%) presented with a low risk of bias; nine studies (69.2%) presented a medium risk of bias, whereas the remaining two studies (15.4%) presented with a high risk of bias (Table 3).[12–24] None of the studies mentioned sample size estimation. Only two studies had mentioned about single operator carrying out all the experiments.[16,20] Only three studies had not mentioned whether included teeth samples were restored or caries-free in the experimental study.[12,13,24] Four studies mentioned the quantity of material that had been used in the experimental protocol.[16–18,20] All the authors followed the manufacturing instructions as given in the product details that were used in their study. In most of the study groups, CPP–ACP was applied over a sound dentin structure. In two studies, CAD groups, and in another two studies, demineralized dentin was used.[12,16,20,22]

Adebayo et al. reported that the Tooth Mousse™ application was not significantly affected. Regardless of the adhesive technique employed, Bahari et al.[13] reported that surface-treating CAD with CPP–ACP had no appreciable impact on bond strength. Four studies measured shear bond strength (SBS), eight studies measured tensile bond strength, and only one research discussed the interfaces between resin and dentin have been studied using field-emission scanning electron microscopes (FE-SEMs).[13–24] According to the results of the study by Barbosa–Martins et al.,[16] pretreating demineralized dentin with remineralizing materials has been shown to be an effective, workable way to improve bonding while according to Doozandeh and Mirmohammadi[12] etching dentin affected by caries for up to 45 seconds could improve its SBS and bring it almost to that of normal dentin (ND). Pretreatment with

**Table 1:** Eligibility criteria used for the study selection

| *Category* | *Inclusion criteria* | *Exclusion criteria* |
|---|---|---|
| Participant/population characteristics. | Studies conducted till 30 November 2020 involving the evaluation of bond strength using a CG and CPP–ACP group is defined as using over dentin with self-etch adhesive restoration.<br>Studies using human premolars and molars as samples. | Articles related to the bond strength of enamel; orthodontic brackets and dentin of primary teeth were excluded from the study. |
| Intervention. | Studies with CPP–ACP. | Studies in which CPP–ACP was not used as an intervention agent. |
| Comparison/CG. | Studies with bond strength assessed using CPP–ACP group/CG on dentin with self-etch adhesives restoration. | Studies are excluded if there is no CG.<br>Before and after studies. |
| Outcome. | Studies showed the strength of self-etch adhesives as measured following the application of CPP–ACP. | Studies showed the strength of etch-and-rinse adhesives, and glass ionomer cement as measured following the application of CPP–ACP. |
| Study design. | *In vitro* studies. | • Case reports.<br>• Case series.<br>• Studies with no statistical analysis comments.<br>• Review articles.<br>• Conference abstract.<br>• Interviews.<br>• Commentaries.<br>• Letters to editor and review. |

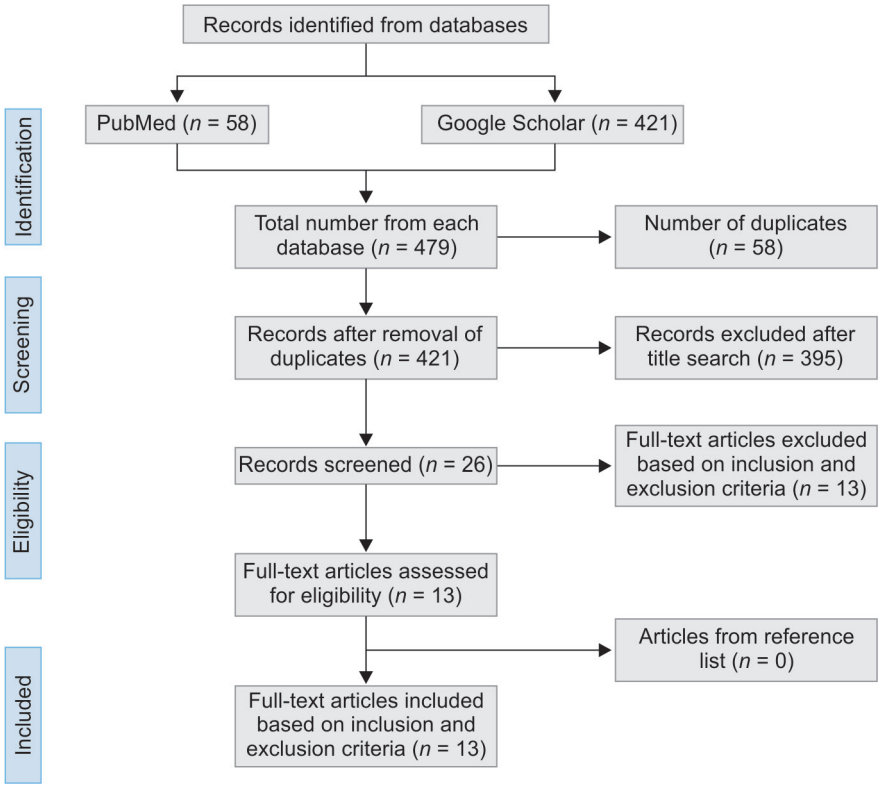


**Fig. 1:** The PRISMA flowchart of the literature search and selection process

MI Paste™ did not significantly affect the SBS of the etch-and-rinse adhesive in CAD. Kamozaki et al.[17] The microtensile bond strength of softened dentin was unaffected by the CPP–ACP-based pastes while Krithi et al.[18] stated that reduction in bond strength when CPP–ACP was used as a remineralizing agent. Pei et al.[19] and Zorba et al.[24] mentioned that the shear bond strength of different adhesive systems used to bond resin composite to dentin is unaffected by the application of different desensitizing agents. Shafiei et al.[20] stated that CPP–ACP increases bond strength when applied before adhesive. Sattabanasuk et al.[21] concluded that CPP–ACP on the dentin surface may improve the bonding performance of self-etch adhesive systems but reduce the effectiveness of etch-and-rinse adhesive systems. According to the findings of the study by Tayal et al.,[22] the binding strength of the CPP–ACP specimens was

**Table 2:** The risk of bias assessment was based on and adapted from a previous study

| *Study* | *Comparison group* | *Random allocation* | *Sample size* | *Teeth free of caries or restoration* | *Manufacturer's instructions* | *Single operator* | *Quantity of material* | *Blinding of the operator* | *Risk of bias* |
|---|---|---|---|---|---|---|---|---|---|
| Adebayo et al.[14] | Y | Y | N | Y | Y | N | N | N | Medium |
| Adebayo et al.[15] | Y | Y | N | Y | Y | N | N | N | Medium |
| Bahari et al.[13] | Y | Y | N | N | Y | N | N | Y | Medium |
| Barbosa–Martins et al.[16] | Y | Y | N | Y | Y | Y | Y | N | Low |
| Doozandeh and Mirmohammadi[12] | Y | Y | N | N | Y | N | N | N | High |
| Kamozaki et al.[17] | Y | Y | N | Y | Y | N | Y | N | Medium |
| Krithi et al.[18] | Y | Y | N | Y | Y | N | Y | N | Medium |
| Pei et al.[19] | Y | Y | N | Y | Y | N | N | N | Medium |
| Shafiei et al.[20] | Y | Y | N | Y | Y | Y | Y | N | Low |
| Sattabanasuk et al.[21] | Y | Y | N | Y | Y | N | N | N | Medium |
| Tayal et al.[22] | Y | Y | N | Y | Y | N | N | N | Medium |
| Torkani et al.[23] | Y | Y | N | Y | Y | N | N | N | Medium |
| Zorba et al.[24] | Y | Y | N | N | Y | N | N | N | High |

N, no; Y, yes

**Table 3:** An overview of the information gathered from the 13 contributing research studies

| *S. No.* | *Authors, country, and year* | *Bond strength measurement* | *Tooth type* | *Group and sample size* | *Adhesive protocol* | *Result and conclusion* |
|---|---|---|---|---|---|---|
| 1. | Adebayo et al.,[14] Australia, 2008 | Micro-SB-SMSBS. | Permanent molar teeth. | *Control*<br>Smear layer retained ($n$ = 22).<br>Smear layer removed using 15% EDTA for 90 seconds ($n$ = 23).<br>*Experimental*<br>CPP–ACP paste (Tooth Mousse treated for 60 minutes daily 7 days.<br>Smear layer retained ($n$ = 22).<br>Smear layer removed using 15% EDTA for 90 seconds ($n$ = 23). | Two self-etching /priming adhesives Clearfil SE Bond™ (CSE) and GB. | *Result*<br>Tooth Mousse did not affect micro-SBS in group I. There was a statistically significant increase in group II with microshear bond strength for CSE on deep dentin ($p$ = 0.002) and a reduction for GB ($p$ = 0.013) on superficial dentin.<br>*Conclusion*<br>Tooth Mousse application did not reduce micro-SBS strength for CSE but significantly reduced micro-SBS for GB. |
| 2. | Adebayo et al.,[15] Australia, 2010 | FE-SEMs FE-SEM of resin–dentin interfaces. | Permanent molar teeth. | *Control*<br>Smear layered (1A) ($n$ = 6).<br>Smear layer was removed using 15% EDTA for 90 seconds (2A) ($n$ = 6).<br>Untreated controls (1A, 2A).<br>*Experimental*<br>Smear layered (1B) ($n$ = 6).<br>Smear layer removed using 15% EDTA for 90 seconds (2B) ($n$ = 6).<br>CPP–ACP-treated specimens (1B, 2B). | (No conditioning); 30–40% phosphoric acid ($H_3PO_4$); 20% polyacrylic acid) bonded with either a 2-step self-etching primer Adhesive.<br>(CSE, Kuraray Medical) or an "all-in-one" adhesive (GB, GC Corporation). | *Result*<br>No difference were found in bonded resin–dentin interface appearance with 2-step adhesive.<br>The "all-in-one" adhesive resulted more areas with bond failures after the polyacrylic acid conditioning; CPP–ACP treatment showed the bond failures were within the hybrid layer.<br>*Conclusion*<br>The adhesive system may affect quality of the bonded resin–dentin interface produced after CPP–ACP treatment. |

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**Table 3:** *(Contd...)*

| S. No. | Authors, country, and year | Bond strength measurement | Tooth type | Group and sample size | Adhesive protocol | Result and conclusion |
|---|---|---|---|---|---|---|
| 3. | Bahari et al.,[13] Iran, 2014 | Microtensile bond strength (μTBS) to CAD. | Permanent molar teeth. | *Control*<br>Sound dentin samples (ND) ($n$ = 13)<br>*Experimental*<br>CAD samples ($n$ = 13)<br>CAD samples treated with CPP–ACP.<br>GC Tooth Mousse, GC EUROPE N.V. ($n$ = 13). | Bonding with the etch-and-rinse adhesive system:<br>Single bond (SB) (3M ESPE, St. Paul, Minnesota, USA) adhesive system<br>Bonding with the self-etch asystem:<br>CSE (Kurraray Medical, Inc., Okayama, Japan) | *Result*<br>Bond strength of both adhesive systems to sound dentin samples was significantly higher than that to CAD ($p < 0.001$) and CAD/CPP ($p < 0.001$).<br>*Conclusion*<br>Surface treatment of CAD with CPP–ACP did not significantly reduce the bond strength irrespective of the adhesive system used. |
| 4. | Barbosa–Martins et al.,[16] Brazil, 2018 | μTBS. | Third molar teeth. | *Control*<br>Sound dentin (without treatment) ($n$ =3).<br>*Experimental* – demineralized dentin (without treatment) ($n$ = 3).<br>Demineralized dentin + treated with 0.1 mL of the sodium fluoride (NaF) solution (1 minute) ($n$ = 3).<br>Demineralized dentin + treated with 0.1 mL of the MI Paste (1 minute); ($n$ = 3).<br>Demineralized dentin + treated with 50 μL of the Curodont™ Repair was applied and left for 5 minutes, then, a $Ca^{2+}$ and $PO_4$ solution for 1 minute ($n$ = 3). | Two different adhesive systems (Adper™ SB) etch and rinse CSE self-etch. | *Result*<br>The highest μTBS averages were found with SB adhesive system for the demineralized dentin treated with P11-4 and CPP–ACP ($p < 0.05$), and they did not significantly differ from each other ($p > 0.05$).<br>The microtensile bond strength values of P11-4 and CPP–ACP were statistically different with sound dentin ($p < 0.05$).<br>*Conclusion*<br>The pretreatment application of remineralizing agents exhibited better options to improve bonding. The promising results showed by increasing the bonding strength with CSE associated with CPP–ACP and Adper SB 2 associated with self-assembling peptide P11-4 or CPP–ACP. |
| 5. | Doozandeh and Mirmohammadi[12] Iran, 2015 | SBS. | Third molar teeth. | *Control*<br>Group 1 (sound dentin, control), the dentin surfaces were etched with 35% phosphoric acid (Scotchbond Universal Etchant, 3M ESPE; St. Paul, USA) for 15 seconds ($n$ = 10).<br>*Experimental*<br>Group II<br>CAD samples etched with 35% phosphoric acid for 15 seconds ($n$ = 10). | Adper SB, (3M ESPE; St. Paul, Minnesota, USA) were applied on the surfaces, gently air-dried, and light cured for 20 seconds (VIP Junior; Bisco, Schaumburg, USA). | *Result*<br>The highest SBS showed by ND groups among different groups. In both the etching times, there were no significant differences between SBS of SB adhesive to CAD with or without CPP–ACP pretreated There was a statistically significant difference between different etching times in CAD groups ($p < 0.05$). |

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**Table 3:** *(Contd...)*

| S. No. | Authors, country, and year | Bond strength measurement | Tooth type | Group and sample size | Adhesive protocol | Result and conclusion |
|---|---|---|---|---|---|---|
| | | | | Group III<br>CAD samples etched with 35% phosphoric acid for 15 seconds treated with CPP–ACP for 3 minutes ($n = 10$).<br>Group-IV CAD samples etched with 35% phosphoric acid for 45 seconds ($n = 10$).<br>Group-V CAD samples etched with 35% phosphoric acid for 45 seconds treated with CPP–ACP for 3 minutes ($n = 10$). | | *Conclusion*<br>MI Paste pretreatment had not significant effect on SBS of etch-and-rinse adhesive in CAD. The extended etching time up to 45 seconds resulted the increase in SBS of CAD and approach nearly to SBS of ND. |
| 6. | Kamozaki et al.,[17] Brazil, 2015 | µTBS. | Third molar teeth. | *Control*<br>CG – Softened dentin with no CPP–ACP treatment ($n = 20$).<br>*Experimental*<br>MP: Softened dentin treated with CPP–ACP paste – MI Paste (GC American Inc., Alsip, Illinois, USA) ($n = 20$).<br>MPP: Softened dentin treated with CPP–ACP + 900 ppm NaF paste – MI Paste Plus (GC American, Inc., Alsip, Illinois, USA) ($n = 20$).<br>Each group was further divided into two subgroups ($n = 10$) according to the laser application protocol. | The self-etching adhesive system CS (Kuraray Medical, Inc., Tokyo, Japan. | *Result*<br>There is significant reduction on bond strength values for the CG treated with laser, as compared with groups that were treated with CPP–ACP-based pastes and laser.<br>*Conclusion*<br>The CPP–ACP based pastes did not affect the microtensile bond strength of softened dentin. |
| 7. | Krithi et al.,[18] India, 2020 | µTBS. | Permanent premolars or molars. | *Control*<br>Group I (sound dentin) ($n = 36$).<br>*Experimental*<br>Group II (demineralized dentin) ($n = 36$).<br>Group III (NaF) ($n = 36$).<br>Group IV (CPP–ACP) ($n = 36$).<br>Group V (NovaMin) ($n = 36$).<br>Group VI (nonfluoridated) ($n = 36$). | Adper SB 2/Plus, 3M ESPE, St. Paul, Minnesota USA.<br>(Subgroup I).<br>Two-step etch-and-rinse adhesive CSE, Kuraray Co. Ltd., Osaka, Japan.<br>(Subgroup II)<br>Two-step self-etch adhesive. | *Result*<br>In Group I, the mean micro-SBS of composite was greater than in groups II-VI under both the adhesives dentin.<br>*Conclusion*<br>The weaker bonds formed by composite to remineralized dentin.<br>NaF and NovaMin achieved greater bond strength to dentin by using a self-etch bonding system. |
| 8. | Pei et al.,[19] China, 2013 | µTBS. | Caries-free third molar teeth. | *Control*<br>No treatment etching with a 1% citric acid solution for 20 s ($n = 8$).<br>*Experimental*<br>Group I: A novel Arg $CaCO_3$ containing polishing paste (Sensitive Pro-Relief; Colgate-Palmolive, New York, USA) ($n = 8$).<br>Group II: A CPP–ACP-containing paste (Tooth Mousse; GC, Tokyo, Japan) was applied to the specimens using an applicator brush and left for 3 minutes ($n = 8$). | One-step self-etch adhesive agents GB (GC, Tokyo, Japan) CSE (Kuraray Medical, Okayama, Japan). | *Result*<br>The desensitizer type significantly influenced microtensile bond strength ($F = 4.10$, $p < 0.05$).<br>CPP–ACP did not affect bonding with S3 or GB.<br>*Conclusion*<br>Calcium-containing pastes might be recommended for improving adhesives and desensitizing effects. |

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**Table 3:** *(Contd...)*

| S. No. | Authors, country, and year | Bond strength measurement | Tooth type | Group and sample size | Adhesive protocol | Result and conclusion |
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| | | | | Group III: An experimental hydroxyapatite paste (particle size < 200 nm; Sigma, St. Louis, Minnesota, USA ($n$ = 8). | | |
| 9. | Shafiei et al.,[20] Iran, 2017 | SBS to CAD. | Third molar teeth. | *Control*<br>Group I<br>The mix Fuji II LC applied over the dentin surface ($n$ = 12).<br>Group III:<br>Control/Vertise flow.0.05 mm applied Vertise flow over dentin surface ($n$ = 12).<br>*Experimental*<br>Group II<br>A 0.01 mL CPP–ACP was applied and then the mix Fuji LII C applied over the dentin surface ($n$ = 12).<br>Group IV:<br>A 0.01 mL CPP–ACP applied and then Vertise flow applied as CG ($n$ = 12). | Bonding with the Fuji II LC adhesive system:<br>(GC Company, Vertise flow adhesive system Kerr manufacturing). | *Result*<br>CPP–ACP significantly increases the bond strength of Fuji LII C and Vertise flow; $p$ < 0.001.<br>*Conclusion*<br>CPP–ACP increases bond strength when applied before adhesive. |
| 10. | Sattabanasuk et al.,[21] Thailand, 2009 | µTBS and scanning electron microscopy. | Permanent molar teeth. | *Control*<br>Group I: No treatment (control).<br>*Experimental*<br>Group II: A CPP–ACP-containing paste, Tooth Mousse, was applied to the dentin surfaces and left in place for 5 minutes.<br>Group III: A CPP–ACP-containing paste was applied and left undisturbed for 5 days to prolong the effect of CPP–ACP on dentin surface. | Bonding with either three-step etch-and-rinse adhesive, OptiBond FL or two-step self-etch adhesive, CSE. | *Result*<br>No statistically significant difference between the two CPP–ACP treated groups ($p$ = 1.000).<br>Bond strengths of CSE to dentin appeared to be similar for all tested groups. OptiBond FL, however, showed lower bond strengths following the application of CPP–ACP for both time periods. Under SEM observations, the CPP–ACP treated dentin displayed a layer of residue or precipitate attached to the surface after the phosphoric acid treatment.<br>*Conclusion*<br>The presence of CPP–ACP on the dentin surface, therefore, may compromise the bonding effectiveness of the etch-and-rinse adhesive system. However, CPP–ACP application may be beneficial to the dentin bonding of self-etch adhesive system. |

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**Table 3:** *(Contd...)*

| S. No. | Authors, country, and year | Bond strength measurement | Tooth type | Group and sample size | Adhesive protocol | Result and conclusion |
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| 11. | Tayal et al.,[22] India, 2013 | Tensile bond strength (TBS). | Mandibular Permanent molars. | *Control*<br>Group III: Samples were restored with GB (GC Corporation, Tokyo, Japan) and composite resin (Filtek Z-350, 3M ESPE).<br>No CPP–ACP applications were done in CG.<br>*Experimental*<br>Group I:<br>Samples were treated with Tooth Mousse (GC Corporation, Tokyo, Japan) for 60 minutes daily for 7 days. No prior etching was done ($n$ = 15).<br>Group III: Same as group II with the application of CPP–ACP, dentin was etched with Scotchbond multipurpose etchant (PA) for 15 seconds, gently rinsed for 10 seconds with an air water spray ($n$ = 15). | GB<br>(GC Corporation, Tokyo, Japan). | *Result*<br>The results clearly show that there was statistically insignificant difference ($p > 0.05$) between the tensile bond strengths of the groups I and III. However, there was statistically significant difference ($p < 0.001$) between the tensile bond strengths of groups II and III.<br>*Conclusion*<br>Tensile bond strength of GB was not significantly reduced after CPP–ACP application, but after prior etching the CPP–ACP specimens, the bond strength of GB was significantly reduced. |
| 12. | Torkani et al.,[23] Iran, 2020 | µTBS. | Third molar teeth. | A total of 90 samples were included in this study and randomly divided into six subgroups ($n$ = 15).<br>Groups I, III, and V No CPP–ACP (CG) Groups II, IV, and VI CPP–ACP application done with (etch and rinse), (self-etch two-step), and (one-step self-etch) adhesives, respectively. | Bonding agents used in this study included. OptiBond Solo Plus (Kerr Corporation, Orange, California, USA) (etch and rinse), CSE (Kuraray Medical, Inc., Okayama, Japan) (self-etch two-step), GB (GC Corporation, Tokyo, Japan) (one-step self-etch). | *Result*<br>There was no significant difference in bond strength of OptiBond Solo Plus ($p$ = 0.44) and CSE ($p$ = 0.67) with/without CPP–ACP.<br>A significant difference was found between the two subgroups of GB in this respect ($p < 0.001$).<br>*Conclusion*<br>The µTBS in use of GB is significantly higher following dentin treatment with CPP–ACP compared with no use of CPP–ACP. |
| 13. | Zorba et al.,[24] Turkey, 2010 | The SBS. | Permanent molars teeth. | *Control*<br>CG: No treatment<br>($n$ = 40).<br>*Experimental*<br>Tooth Mousse: Tooth Mousse gel was applied to dentinal surfaces using an applicator brush ($n$ = 40).<br>Cervitec Plus: Cervitec Plus varnish was applied to dentinal surfaces using an applicator and dispersed with air 30 seconds after application UltraEZ: UltraEZ was applied to dentinal surfaces and left standing overnight ($n$ = 40). | XP Bond Dentsply DeTrey GMBH, Twostep total etch dentin bonding agent.<br>AdheSE Ivoclar Vivadent.<br>Two-step selfetch dentin bonding agent.<br>Adper Prompt LPop.<br>3M Dental Products. | *Result*<br>With the exception of the Control/AdheSE and UltraEZ/XP Bond groups, no statistically significant differences were found in the SBS values of the groups tested.<br>*Conclusion*<br>The use of different desensitizing agents does not affect the SBS of various adhesive systems used to bond resin composite to dentin. |

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**Table 3:** *(Contd...)*

| S. No. | Authors, country, and year | Bond strength measurement | Tooth type | Group and sample size | Adhesive protocol | Result and conclusion |
|---|---|---|---|---|---|---|
| | | | | Next, each group of the specimen was randomly divided into four subgroups ($n$ = 10) to evaluate the effects of different bonding systems.<br>G-Bond, GC International, one-step selfetch dentin bonding agent. | Onestep selfetch dentin bonding agent. | |

EDTA, ethylenediaminetetraacetic acid; ND, normal dentin; MPP, MI paste plus; PA, post application

considerably decreased following previous etching. According to Torkani et al.,[23] the microtensile bond strength when using G-Bond™ (GB) is noticeably stronger after dentin treatment with CPP–ACP as opposed to when CPP–ACP is not used.

As this is the first comprehensive analysis of how CPP–ACP affects the strength of self-etch adhesives' bond with dentin. The fact that the authors conducted the review in accordance with the PRISMA guidelines is another strength of the study.

One limitation is that the variability among the included studies regarding their methodology, such as CPP–ACP and adhesive application protocol (e.g., different comparative groups, etchant concentration, and time application). In none of the research studies, a sample size calculation is done. Furthermore, the study's teeth's caries-free and repaired categories lacked uniformity in the selection process. Only two studies methodology performed by a single operator and one study in which blinding of the operator was done to reduce inter-operator bias.[13,16,20] Because of the inconsistent approaches and impossibility of comparing the different therapies used and the different study designs of the included studies, a meta-analysis was not advised. Restricted access for searching numerous databases is another study drawback.

## Conclusion

The study's results and risk of bias evaluation indicated that the current review study's risk of bias was medium. The degree of variance among the included research makes it impossible to draw conclusions about how CPP–ACP application affects dentin's ability to bind to self-etch adhesives.

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## References

1. Azarpazhooh A, Limeback H. Clinical efficacy of casein derivatives: A systematic review of the literature. J Am Dent Assoc 2008;139(7):915–924. DOI: 10.14219/jada.archive.2008.0278.
2. Divyapriya GK, Yavagal PC, Veeresh DJ. Casein phosphopeptide–amorphous calcium phosphate in dentistry: An update. Int J Oral Health Sci 2016;6(1):18. DOI: 10.4103/2231-6027.186660.
3. Gagnaire V, Pierre A, Molle D, et al. Phosphopeptides interacting with colloidal calcium phosphate isolated by tryptic hydrolysis of bovine casein micelles. J Dairy Res 1996;63(3):405–422. DOI: 10.1017/s0022029900031927.
4. Llena C, Forner L, Baca P. Anticariogenicity of casein phosphopeptide–amorphous calcium phosphate: A review of the literature. J Contemp Dent Pract 2009;10(3):1–9. PMID: 19430620.
5. Reynolds EC. Remineralization of enamel subsurface lesions by casein phosphopeptide-stabilized calcium phosphate solutions. J Dent Res 1997;76(9):1587–1595. DOI: 10.1177/00220345970760091101.
6. Al Batayneh O. Clinical applications of Tooth Mousse™ and other CPP–ACP products in caries prevention: Evidence-based recommendations. Smile Dent J 2009:4(1):8–12. Available from: htttps://www.researchgate.net/publication/220042410_The_clinical_applications_of_Tooth_Mousse_TM_and_CPP-ACP_products_in_caries_prevention_evidence-_based_recommendations.
7. Cao Y, Mei ML, Xu J, et al. Biomimetic mineralisation of phosphorylated dentine by CPP–ACP. J Dent 2013;41(9):818–825. DOI: 10.1016/j.jdent.2013.06.008.
8. Giannini M, Makishi P, Ayres AP, et al. Self-etch adhesive systems: A literature review. Braz Dent J 2015;26(1):3–10. DOI: 10.1590/0103-6440201302442.
9. Farooq I, Moheet IA, Imran Z, et al. A review of novel dental caries preventive material: Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) complex. King saud university J Dent Sci 2013;1;4(2):47–51. DOI: DOI: 10.1016/j.ksujds.2013.03.004.
10. AlShwaimi E, Bogari D, Ajaj R, et al. *In vitro* antimicrobial effectiveness of root canal sealers against *Enterococcus faecalis*: A systematic review. J Endod 2016;42(11):1588–1597. DOI: 10.1016/j.joen.2016.08.001.
11. Cross KJ, Huq NL, Reynolds EC. Casein phosphopeptides in oral health-chemistry and clinical applications. Curr Pharm Des 2007;13(8):793–800. DOI: 10.2174/138161207780363086.
12. Doozandeh M, Mirmohammadi M. The simultaneous effect of extended etching time and casein phosphopeptide–amorphous calcium phosphate containing paste application on shear bond strength of etch-and-rinse adhesive to caries-affected dentin. J Contemp Dent Pract 2015;16(10):794–799. DOI: 10.5005/jp-journals-10024-1759.
13. Bahari M, Oskoee SS, Kimyai S, et al. Effect of casein phosphopeptide–amorphous calcium phosphate treatment on microtensile bond strength to carious affected dentin using two adhesive J Dent Res Dent Clin Dent Prospects 2014;8(3):141. DOI: 10.5681/joddd.2014.026.
14. Adebayo OA, Burrow MF, Tyas MJ. Dentine bonding after CPP–ACP paste treatment with and without conditioning. J Dent 2008;36(12):1013–1024. DOI: 10.1016/j.jdent.2008.08.011.
15. Adebayo OA, Burrow MF, Tyas MJ. Resin–dentine interfacial morphology following CPP–ACP treatment. J Dent 2010;38(2):96–105. DOI: 10.1016/j.jdent.2009.09.007.
16. Barbosa–Martins LF, de Sousa JP, de Castilho AR, et al. Enhancing bond strength on demineralized dentin by pre-treatment with selective remineralising agents. J Mech Behav Biomed Mater 2018;81:214–221. DOI: 10.1016/j.jmbbm.2018.03.007.

17. Kamozaki MB, Prakki A, Perote LCCC, et al. The effect of CPP–ACP and Nd:YAG laser on the bond strength of softened dentin. Braz Oral Res 2015;29:S1806-83242015000100268. DOI: 10.1590/1807-3107BOR-2015.vol29.0068.
18. Krithi B, Vidhya S, Mahalaxmi S. Microshear bond strength of composite resin to demineralized dentin after remineralization with sodium fluoride, CPP–ACP and NovaMin containing dentifrices. J Oral Biol Craniofac Res 2020;10(2):122–127. DOI: 10.1016/j.jobcr.2020.03.007.
19. Pei D, Liu S, Huang C, et al. Effect of pretreatment with calcium-containing desensitizer on the dentine bonding of mild self-etch adhesives. Eur J Oral Sci 2013;121 (3 Pt 1):204–210. DOI: 10.1111/eos.12047.
20. Shafiei F, Derafshi R, Memarpour M. Bond strength of self-adhering materials: Effect of dentin-desensitizing treatment with a CPP–ACP paste. Int J Periodontics Restorative Dent 2017;1;37(6):337–343. DOI: 10.11607/prd.2850.
21. Sattabanasuk V, Burrow MF, Shimada Y, et al. Resin bonding to dentine after casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) treatments. J Adhes Sci Technol 2009;1;23(7–8):1149–1161. DOI: 10.1163/156856109X432686.
22. Tayal SC, Dhillon J, Tayal A. Effect of prior etching on bond strength of self-etch adhesive in case of sensitive teeth treated with CPP–ACP. Dent J Adv Stud 2013;1(01):009–014. DOI: 10.1055/s-0038-1670585.
23. Torkani MA, Mesbahi S, Abdollahi AA. Effect of casein phosphopeptide amorphous calcium phosphate conditioning on microtensile bond strength of three adhesive systems to deep dentin. Front Dent 2020;17:34. DOI: 10.18502/fid.v17i34.5198.
24. Zorba YO, Erdemir A, Ercan E, et al. The effects of three different desensitizing agents on the shear bond strength of composite resin bonding agents. J Mech Behav Biomed Mater 2010;3(5):399–404. DOI: 10.1016/j.jmbbm.2010.03.003.