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## Strategies to optimize bonding of adhesive materials to molar-incisor hypomineralization-affected enamel: A systematic review

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## TITLE PAGE

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**STRATEGIES TO OPTIMISE BONDING OF ADHESIVE MATERIALS TO MOLAR-INCISOR  
HYPOMINERALIZATION-AFFECTED ENAMEL: A SYSTEMATIC REVIEW**

**ABSTRACT**

Background: Children with first permanent molar affected by Molar-Incisor Hypomineralization (MIH) show high treatment failure rate.

Aim: To conduct a systematic review on bonding of adhesive materials to MIH-affected enamel, so as to identify all the methods suggested to optimise it and to determine the best bonding protocol(s).

Design: An exhaustive literature search was conducted on Medline/PubMed, the Cochrane Library and Web of Sciences databases, up to October 2018. Laboratory and clinical studies, involving adhesive restorations bonded to MIH-affected enamel, with at least a comparative group were included. Two authors independently selected studies, collected data and assessed bias risk.

Results: After titles and abstracts review and duplicates exclusion, 14 articles were selected on the 496 eligible papers. After full reading, 4 articles were excluded. Finally, 10 studies (6 laboratory and 4 clinical studies) were included.

Conclusions: Bond strength of composite was not significantly different when using self-etch compared with etch-and-rinse adhesives. Deproteinization after etching for etch-and-rinse adhesives enhanced bond strength; this could allow to keep MIH-affected enamel. Icon® showed an erratic penetration, however a preliminary deproteinization after etching could improve bond strength. A study reported no

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significant differences in sealant retention rate, whereas another recommended to previously apply an adhesive.

**KEY WORDS:** MIH, bonding, bond strength, adhesive, deproteinization, resin infiltration

## INTRODUCTION

Molar-Incisor Hypomineralization (MIH) is a qualitative enamel defect of systemic origin, of one to four first permanent molars, and often combined with permanent incisors [1]. Its prevalence ranges between 2.5% and 40% according to the studies [2]. A recent meta-analysis yields a global mean prevalence of 12.9% and a global incidence of 17.5 million people in 2016 [3].

The defects are clinically characterized by demarcated opacities, of various colors (white, yellow or brown) and extend (small to large areas), and frequently undergo post-eruptive breakdown [1]. They microscopically correspond to less dense prism structure with loosely arranged apatite crystal and larger prism sheaths [4,5], with a significant reduced mineral density in regards to sound enamel [6], possibly due to retained proteins during enamel maturation. As a consequence, MIH-affected enamel exhibits lower mechanical properties, with weaker hardness and modulus of elasticity, against sound enamel [7]. Porous enamel structure and enamel breakdown lead to hypersensitivity and/or exposed dentin and carious lesion development [8,9].

Moreover, it was reported that MIH-affected children required more treatment and showed higher treatment failure rate when compared with non-affected children: Kotsanos et al. [10] revealed that restorative intervention was 11-fold greater in children with MIH and that sealants and fillings needed three times more re-treatment than in children without MIH. Likewise, Jälevik et al. [11] found that MIH-affected children had almost ten times more treatment and often had repeated treatments. All laboratory studies also highlighted the weaker bond strength of resin composite to MIH-affected enamel [12] and the failure of phosphoric acid to create etching patterns, compared with sound enamel [13].

It would be relevant to determine how to improve adhesion to MIH-affected enamel, to improve the longevity of restoration of these affected teeth.

The objective of this study was to conduct a systematic review on bonding of adhesive materials to MIH-affected enamel, so as to identify all the suggested methods to optimise the bonding to this hypomineralized enamel and to determine which is (are) the best bonding protocol(s).

## MATERIAL AND METHODS

This systematic review was implemented according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [14].

### Search strategy

An exhaustive literature search was carried out on the electronic databases Medline/PubMed, the Cochrane Library and Web of Sciences. The search equation, for the three databases, was built from

keywords related to MIH combined with keywords related to bonding. This equation was structured as follows: (mottled enamel OR non-endemic mottling of enamel OR internal enamel hypoplasia OR cheese molars OR non-fluoride enamel opacities OR idiopathic enamel opacities OR enamel hypomineralization OR enamel hypomineralisation OR hypomineralized molars OR hypomineralised molars OR molar incisor hypomineralization OR molar incisor hypomineralisation OR MIH) AND (bond strength OR bonding OR retention OR survival OR longevity OR infiltration). The last search date was in October 2018. In addition, all the references of the selected articles were checked, to identify other relevant papers.

Titles and abstracts were screened by two independent reviewers (ML, ED). Irrelevant studies, unrelated to bonding to MIH-affected enamel, were excluded. In case of difference, a consensus was decided by a supervisor (JPA). Then, full texts of all potentially eligible papers were assessed according to inclusion criteria. Inclusion or exclusion of studies was independently decided by the two reviewers (ML, ED). In case of difference, a consensus was also decided by the supervisor (JPA).

### **Inclusion criteria**

Eligible studies had to be laboratory or clinical study related to bonding to MIH-affected enamel. No language or date restrictions were applied.

Inclusion criteria were: studies involving adhesive materials (including resin composite, glass ionomer cement, sealant and resin infiltration) bonded to MIH-affected, with at least a comparative group (involving bonding to sound enamel or to MIH-affected enamel with another bonding protocol).

Exclusion criteria were: irrelevant studies (not dealing with bonding of adhesive materials to MIH-affected teeth), case reports, case series without controls, reviews, studies relating a treatment technique, studies on animals.

### **Data extraction and analysis**

For each paper, the data were collected independently by the two reviewers (ML, ED). For laboratory studies, the number of sound and MIH-affected teeth, the severity of the MIH (if stated), the tooth storage media, the materials used, the bonding protocol, the tests performed and the results were recorded. For clinical studies, the study design, the number and age range of patients, the number of MIH-affected teeth, the control group, the severity of the MIH (if stated), the materials used, the bonding protocol, the follow-up and the results were recorded. In case of difference, a consensus was decided by the supervisor (JPA). Owing to the studies heterogeneity, no meta-analysis could be achieved, but study characteristics and results were qualitatively analysed.

### **Study quality assessment**

The methodological quality of the laboratory and clinical studies was independently evaluated by the two reviewers (ML, ED). Differences were resolved with the supervisor (JPA).

The quality assessment of each included laboratory study was based and adjusted from previous systematic reviews of laboratory studies [15,16]. The risk of bias was assessed as per the following items: teeth randomization, indication on MIH severity, presence of a control group, similar sample size, protocol clearly described, blinding of the tests' operator, sample size calculation and statistical analysis. If the authors reported the item, the study received a "yes" on the item; if there was no information, the study received a "no." For one to three "yes", the study was considered as "high risk of bias"; for four or five "yes", the study was considered as "medium risk of bias"; for six to eight yes, the study was considered as "low risk of bias".

The quality assessment of each included clinical study was based on the Cochrane Risk Bias tool [17]. The latter addressed six items: random sequence generation, allocation concealment, blinding of participants and personnel (which we divided into two parts: blinding of participants and blinding of personnel), blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases (sample size, presence of a control group). Following recommendations of the Cochrane Handbook, each item received a "yes" if the parameter was respected, a "no" if not and an "unclear" if information was lacking. Studies with at least one "no" were classified as "high risk of bias" (except for blinding of personnel and for the other biases); studies with "unclear" for one or more domains were classified as "unclear risk of bias" (except for blinding of personnel and for the other biases); and studies with "yes" in all domains were classified as "low risk of bias".

## **RESULTS**

### **Study selection**

The initial search found 496 eligible papers from Medline/PubMed, the Cochrane Library and Web of Sciences. After titles and abstracts review and exclusion due to duplication, 14 articles were selected. After full reading, 4 articles were excluded, because of the absence of control group (i.e. no comparison with sound teeth or another bonding protocol). Finally, 10 studies were included: 6 laboratory studies [18,19,20,21,22,23] and 4 clinical studies [24,25,26,27] (tables 1 and 2). The process of article selection is summarized in figure 1. Risk of bias in the included studies is summarized in figure 2.

### **Study characteristics**

Among the six laboratory studies: all of them used sound and MIH-affected extracted teeth [18,19,20,21,22,23]. Five of them indicated severity of hypomineralization, by mentioning the colour of the hypomineralized area or deeper damage (creamy-white or yellow-brown [18,19,20], up to moderate appearance [22], post-eruption breakdown of enamel and failed restoration [23]). Four of them involved bonding of resin composites, another involved bonding of sealants and the last involved Icon® resin infiltration. Three studies evaluated the quality of adhesion by microshear bond strength tests, followed by failure mode analysis [23]; one used micro-tensile bond strength tests, followed by failure mode analysis [22]; two examined Icon® infiltration of MIH-affected enamel, by light microscopy [19] or confocal laser scanning microscopy [22]; and one study assessed the microhardness changes for MIH lesions treated with Icon® [19].

Among the four clinical studies: all of them were prospective (of which three randomized [24,26,27]) studies: two studies during 18 months of follow-up [24,25], one during 24 months [27] and one during 48 months [26]. All of them involved experienced operators, calibrated examiners and blinded examination. Three of them enrolled patients aged 6-8 years [24, 25,26] and the fourth enrolled patients aged 8-12 years [27]. All indicated severity of hypomineralization, although only one analyzed its influence [25]. Two of them reported the success rate of resin composite restorations [24,27] and two that of sealants [25,26]: three used modified US Public Health Service (USPHS) criteria [24,25,27] and one only the sealant retention [26]. Two had a control group including teeth without MIH [24,27] and two compared different bonding protocols on MIH-affected teeth [25,27].

Through these laboratory and clinical studies, different bonding protocols were suggested to improve adhesion to MIH-affected enamel. Three studies compared various types of adhesives (etch-and-rinse adhesives, self-etch adhesives or universal adhesives) [22,23,24]; six studies used deproteinization procedure (application of sodium hypochlorite (NaOCl) or Papacarie®) [18,19,20,21,22,27]; three studies tested the interest of resin infiltration (Icon®) and its combination with deproteinization [18,19,22].

#### **Bonding results according to the enamel substrate**

Except Fragelli et al. [25], all laboratory or clinical studies comparing bonding to MIH-affected enamel with bonding to sound enamel, reported significantly less bond strength to MIH-affected enamel [18,20,22,23,27]. In fact, Fragelli et al. [25] reported no significant differences of the sealant retention rate on MIH-affected enamel and sound enamel (72% vs 62% respectively).

In laboratory studies, William et al. [23] described higher cohesive failures in hypomineralized enamel (whatever the adhesive used) compared to sound enamel. Likewise, Chay et al. [18] and Ekambaram et al. [20] noted cohesive failures only in MIH-affected enamel.

Moreover, clinically, Sönmez et al. [27] evaluated two different cavity designs for resin composite restorations: an “invasive treatment” with the removal of all the affected enamel to obtain margins in



sound enamel; a “non-invasive treatment” with the removal of affected enamel until the bur met with significant resistance from the hypomineralized enamel. Success rate at 24 months of non-invasive treatment was significantly lower, with marginal cracks, compared with invasive treatment and sound enamel (58.6% vs 81.3% and 87.1% respectively).

Severity of hypomineralization also could influence bond strength, even if Chay et al. [18] and Ekambaram et al. [20] for composites and Fragelli et al. [25] for sealants reported no significant differences according to the enamel colour.

### **Bonding results for resin composites according to the protocol**

#### *Type of adhesives*

William et al. [23], Krämer et al. [22] and de Souza et al. [24] compared the use of a self-etch adhesive (Clearfil™ SE Bond) with a etch-and-rinse adhesive (Optibond™ FL [22], 3M™ Single Bond [23], Adper™ Scotchbond™ Multipurpose [24]) or a universal adhesive (Scotchbond™ Universal [22]). In their laboratory study, William et al. [23] found no significant differences between the etch-and-rinse and the self-etch adhesives (Clearfil™ SE Bond 10.4 MPa vs 3M™ Single Bond 7.1 MPa). However, Krämer et al. [22] observed a significant higher bond strength with an etch-and-rinse adhesive compared with a self-etch adhesive and also with a universal adhesive after etching (Optibond™ FL 21.3 MPa vs Clearfil™ SE Bond 11.3 MPa and Scotchbond™ Universal 16.8 MPa). Clinically, de Souza et al. [24] reported no significant differences in success rate at 18 months between the etch-and-rinse and the self-etch adhesives (68% Clearfil™ SE Bond vs Adper™ Scotchbond™ Multi-Purpose 54%).

Besides, William et al. [23] observed no association between failure modes and adhesive type. However, cohesive failures in MIH-affected enamel varied according to the studies between etch-and-rinse adhesives (Adper™ Single Bond 2: 50% [20]; Optibond™ FL: 16% [22]; 3M™ Single Bond: 50% [23]) and self-etch adhesives (Clearfil™ SE Bond 9.5% [20]; Clearfil™ SE Bond 3% [22]; Clearfil™ SE Bond 52% [23]).

#### *Deproteinization*

In laboratory studies, Chay et al. [18] showed that application of NaOCl after etching significantly increased bond strength to MIH-affected enamel, whatever its severity (creamy-white or yellow-brown specimens). Ekambaram et al. [20] also reported a significant increase of bond to MIH-affected enamel when using NaOCl after etching, but also with Papacarie® (NaOCl 24.3 MPa and Papacarie® 24.6 MPa vs 18.6 MPa for MIH-affected and 29.5 MPa for sound enamel). Both reduced the number of enamel cohesive failures. However, they noted that deproteinization significantly improved bond strength to creamy-white samples, in regards to no treatment, whereas there were not significant differences for yellow-brown defect specimens. On the contrary, Krämer et al. [22] reported that a NaOCl pre-treatment

of affected enamel did not enhance enamel bonding, but caused less pre-test failures (NaOCl 23.6 MPa vs MIH-affected enamel 21.3 MPa and sound enamel 31.2 MPa). Likewise, Gandhi et al. [21] reported that NaOCl was not beneficial, but they used it before etching.

Clinically, Sönmez et al. [27] found a significantly higher survival rate at 24 months of resin composites when using NaOCl on MIH-affected enamel (78.12% vs 58.06%), whereas they observed no differences before 12 months.

#### *Resin infiltration*

Icon® infiltration in MIH-affected enamel was only analysed in laboratory studies. Crombie et al. [20] reported an erratic penetration. Krämer et al. [22] showed a poor penetration and found no significant differences in bond strength and failure pattern when NaOCl was applied after etching and before Icon® infiltration. On the contrary, Chay et al. [18] reported a significantly higher bond strength when NaOCl was applied after etching compared without NaOCl, but no difference in failures modes.

#### **Bonding results for sealants according to the protocol**

In their laboratory study, Gandhi et al. [21] found no difference in tags quality when NaOCl was applied before etching on MIH-affected enamel, but a significant difference in favour for etching before sealing. Clinically, Fragelli et al. [25] reported no difference success rate at 18 months between sealant bonded to MIH-affected enamel in regards to those bonded to sound enamel. On MIH-affected enamel, Lygidakis et al. [26] revealed a higher sealant retention at 48 months, when bonded after the application of 5<sup>th</sup> generation adhesive (i.e. a two-step etch-and-rinse adhesive).

#### **Quality assessment**

Among the 10 studies included, 4 exhibited a low risk of bias [20,21,24,27], 4 showed a medium risk [22,18,19,23] and 2 exhibited a high risk of bias [25,26] (fig. 3 and 4). Laboratory studies were badly scored in sample size calculation and blinding of the tests' operator, whereas all clinical studies were found adequate for the blinding of outcome assessment. One clinical study did not perform randomization and allocation of patients [25].

### **DISCUSSION**

#### **The variability between studies**

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Tooth storage media varied according to the study with: chloramine T for three studies [18,22,23], thymol [20], ethanol [21], and 100% humidity; teeth were sometimes previously immersed in: chlorhexidine [18], formaldehyde [19] or buffered formalin [23]. Most of the authors did not justify their choice. Yet, these solutions could change or interact with the enamel microstructure: formaldehyde can bind to proteins, thus prone to inhibit protein removal by deproteinization; or ethanol can dehydrate and thus change the enamel microstructure. The storage temperature and the immersion time were not always mentioned. The latter could possibly impact the enamel microstructure.

The enamel surface also differed according to the studies. In laboratories studies, the enamel surface was grounded from 180 to 600 grits and can involve the end of enamel prism rods or their length: these two parameters may influence the bond strength values. Chay et al. [18] indicated that their specimens surface comprised the ends of the enamel prism rods. William et al. [23] investigated enamel etched surfaces, sectioned perpendicular and parallel to enamel rods and showed different etching patterns, with less dissolution for parallel section. No information was given by the clinical studies. Nevertheless, composite clinically bonds to both the end and the length of the prism rods in a same cavity.

The MIH severity has probably an impact on bond strength or restorative treatment success. One study did not mention it [21]. Some authors defined it as creamy white or yellow brown, whereas others distinguish white, yellow and brown opacities, with or without enamel breakdowns or others spoke about mild or severe defects. The use of a standardized terminology would be relevant [28]. Colour differences were associated with variations in porosity and hardness. The severity can also vary within a tooth. Some authors underlined that their wide standard deviations may reflect enamel differences between teeth and within specimens [18,23]. Most of the studies reported a too small tooth number of each colour to demonstrate a relation between the colour and the bonding and/or the success rate [18,19,20]. Finally, the hypomineralization defects do not involve necessarily the full enamel thickness. In their laboratory study, William et al. [23] highlighted one very high bond strength value for composite bonded to hypomineralized enamel and suggested that the composite was bonded to superficial, fully mineralized enamel overlying deeper hypomineralized enamel, located closer to the dentin-enamel junction. Furthermore, in their clinical studies, Souza et al. [24] and Fragelli et al. [25] weekly applied fluoride varnish during one month before bonding the sealant or the composite. de Souza et al. [24] also placed a glass ionomer as provisional restoration during two months, then removed it partially before bonding the composite. These procedures may increase bond strength, due to an enamel remineralization.

Regarding materials, the products used and protocols were not always the same from one study to the other. Etch-and-rinse adhesives were three- or two-step adhesives, with hydrophilic or hydrophobic monomers. Self-etch adhesives can present various pH and thus differently interact with enamel. In the same way, the concentration of NaOCl and the moment of its application varied according to the studies. Likewise, studies used phosphoric acid instead of the Icon®-etch. Besides, in their clinical studies,

Lygidakis et al. [26] used cotton roll isolation, whereas Fragelli et al. [25] preferred rubber dam to place sealants, that may also influence the success rate.

Finally, shearing methods were not the same according to the laboratory studies: three studies performed micro-shear bond strength tests [18,20,23] and one study used micro-tensile bond strength tests [22]. This is the reason why it was not possible to subject bond strength values to a meta-analysis.

### **The need and the means to improve bond strength to MIH-affected teeth**

#### *Is bonding to MIH-affected enamel lower than to sound enamel?*

Except one, all laboratory and clinical studies clearly highlighted lower bond strength values to MIH-affected enamel. This may be attributed to uneven etching pattern, reduced microtag within the prism rod, less dense enamel prism retaining moisture and increased protein content.

Only Fragelli et al. [25] reported no significant difference in sealant success rate when bonded to sound or MIH-affected enamel after 18-months follow-up. All the same, they noted a lower success rate (even if non-significant) for MIH-affected enamel and recognized themselves that a larger sample size may reveal significant differences. They added that failures often involved retention, secondary caries, marginal adaptation and discoloration can also suggest the bonding difficulties to MIH-affected enamel. Moreover, before sealant placement, they proceeded of weekly fluoride varnish application during one month, that may remineralize the enamel surface and thus increase the sealant adherence.

Furthermore Sönmez et al. [27] showed that an “invasive treatment”, involving the removal of all the affected hypomineralized enamel, allowed a significant higher survival rate of resin composite than an “non-invasive treatment”, keeping the hypomineralized enamel resistant to the bur. This “invasive treatment” gave a similar bond strength than sound enamel. Therefore, when it is possible, a total removal of the defective enamel would ensure a better adhesion. To be more conservative, in particular in case of extended MIH lesions, other means should be implemented to improve bond strength to hypomineralized enamel. However, the latter may proceed to chip away. In fact, laboratory studies highlighted that cohesive failure was frequently observed when bonding to MIH-affected enamel and clinical studies showed that MIH-affected enamel tended to break down around the margin of the restoration. The mechanical properties of the lesion, and not only the adhesive strength, have an influence on the longevity of resin composite restorations. Thus, hardness, fracture resistance and solubility of treated MIH-affected teeth need further investigation.

#### *Which type of adhesive should be preferred?*

William et al. [23] reported no significant differences in bond strength with self-etch adhesives in regards to etch-and-rinse adhesives, as well as de Souza et al. [24] who clinically confirmed no significant differences in success rate of composite bonded with a self-etch adhesive compared with an etch-and-

rinse adhesive after 18 months. However, William et al. [23] suggested that two-step etch-and-rinse adhesives could possibly form inadequate micro-tags, due to little intercrystal porosity and that phosphoric acid etching could increase the mineral loss in regards to self-etch adhesives. Besides, the absence of rinsing of self-etch adhesives could possibly eliminate the interference of residual water on the bond or dilution of water-soluble primer. They could also promote the adhesion due to an additional chemical bonding to hydroxyapatite.

On the contrary, Krämer et al. [22] observed a significant higher bond strength with an etch-and-rinse adhesive in regards to a self-etch adhesive. Several reasons could explain this difference. First, the difference of the MIH severity: William et al. [23] and de Souza et al. [24] achieved their studies with “yellow-brown demarcated opacity” and “severe MIH” respectively, whereas Krämer et al. [22] qualified the MIH severity by “an enamel up to moderate appearance”, more closely resembling to sound enamel. But de Souza et al. [24] bonded the composite after fluoration and temporary glass ionomer placement, that would remineralize the enamel surface and increase bond strength. Second, Krämer et al. [22] reported 15% and 37% of pre-test failures, for etch-and-rinse and self-etch adhesive respectively, that could distort the results. Finally, the three studies used the same self-etch adhesive, but not the same etch-and-rinse adhesive. Krämer et al. [22] used a three-step etch-and-rinse adhesive (Optibond™ FL), with a hydrophobic primer, while William et al. [23] used a two-step etch-and-rinse adhesive (3M™ Single Bond) containing hydrophilic monomers, prone to be diluted by the excess.

Besides, Lygidakis et al. [26] suggested that the acetone of some etch-and-rinse adhesives may remove the residual water of the etched enamel, improving the availability for bonding enamel surface. No study comparing self- and etch-and-rinse adhesives used such acetone-based adhesives.

Only Krämer et al. [22] tested a universal adhesive after etching and reported less bond strength than etch-and-rinse system. A previous study noted that the 10-methacryloyloxydecylidihydrogen phosphate (MDP) forms a stable calcium salt within the hydroxyapatite lattice [29]. The lower calcium content of hypomineralized enamel could possibly reduce chemical adhesion and bond strengths of universal adhesive, containing MDP.

It can be concluded that self-etch adhesives should be interesting to use when bonding to MIH-affected teeth, in particular in case of severe hypomineralization, that would be explained by a higher water content of enamel, more similar to dentin. Further studies are necessary to confirm this hypothesis. They can also be beneficial because of their less demineralization and thus less postoperative sensitivity. Since different self-etch adhesives may vary in acidity (pH), other self-etch adhesives need to be investigated. Further studies are also needed to test universal adhesives without etching, on different severity of MIH.

*Is deproteinization effective to enhance bond strength?*

The increased protein content of MIH-affected enamel reduced the micro-mechanical adhesion. Therefore, it would be relevant to withdraw protein surplus content to enhance adhesion. The oxidizing NaOCl is already employed for dissolving organic material in endodontics [30] and was suggested to increase enamel bond strength in hypocalcified amelogenesis imperfecta [31].

Chay et al. [18], Ekambaram et al. [20] and, clinically, Sönmez et al. [27] reported a significant increase of bond strength to MIH-affected teeth or of survival rate of composite when NaOCl was applied during 60 seconds after etching, whereas Gandhi et al. [21], as Krämer et al. [22] observed no increase of enamel bonding,

The moment of the NaOCl application, before or after etching, could be critical. Saroglü et al. [31] postulated that etching refined enamel access, thus ease protein degradation by NaOCl, making enamel crystals more accessible to the adhesive, thus improving bond strength. Moreover Crombie et al. [20] reported a probable higher enamel microhardness when NaOCl was used in combination with Icon® resin infiltration, after etching (they only used a 0.95% solution). This explains why Gandhi et al. [21], using NaOCl before etching, did not find better resin tags with NaOCl, as Faria-e-Silva et al. [32] did not find better bond strengths to enamel affected by *amelogenesis imperfecta*, when using NaOCl before etching.

Krämer et al. [22] reported no enhanced enamel bond strength, but less pre-test failures, when using NaOCl after etching. They used a three-steps etch-and-rinse adhesive whereas the other studies used for Chay et al. [18], Ekambaram et al. [20] and Sönmez et al. [27]: a two-step self-etch adhesive after etching without the primer with two coats of resin, a two-step etch-and-rinse with two coats of resin, a one-step self-etch adhesive after etching, respectively. Therefore, this study is the only one applying a hydrophilic primer followed by a hydrophobic adhesive after NaOCl and with only one coat of resin. The hydrophobic adhesive would probably have difficulties to infiltrate the wet hypomineralized enamel, despite the NaOCl effect. Two coats of adhesive would be mandatory because of the absorption of the first coat by the porous MIH-affected enamel.

However, Ekambaram et al. [20] underlines that 5% NaOCl may affect oral soft tissues in case of contact and may cause pulp inflammation, especially in young permanent molars, due to their large pulp chamber. An alternative agent would be profitable. Yet, they reported similar results for Papacarie®, which is a papain-based gel containing chloramine, toluidine blue, salts, preservatives, stabilizers, thickener and deionized water [33]. Moreover, Papacarie® may help in chemomechanical caries removal if necessary.

It would be relevant to evaluate the impact on bond strength of reduced NaOCl concentrations, and also compare the use of etch-and-rinse and self-etch adhesives after deproteinization with Papacarie®.

#### *Is the Icon® effective to enhance bond strength?*

Resin infiltrant was designed to penetrate into the non-cavitated carious lesions, and stop its progression by the sealing of porous channels and impede the acid penetration [34]. All studies tented to

report the erratic or poor penetration of Icon® in MIH-affected enamel, regardless whether etching was performed by phosphoric [18,19] or hydrochloric acid (Icon®-infiltrant) [21]. Chay et al. [18] highlighted a great variability of the bond strength values, i.e. large standard deviations, when using Icon®, possibly also indicating its inconsistent penetration. This can be explained by a more or less thick layer of sound enamel above the hypomineralized enamel, impeding Icon® penetration, in particular when using phosphoric acid. However, no studies compared the effect of using phosphoric or hydrochloric acid on bond strength and this warrants further investigation. It would also be relevant to compare the microhardness of enamel infiltrated by Icon® and sound enamel, that no study evaluated.

*Is the combination of these propositions effective to enhance bond strength?*

Chay et al. [18] and Sönmez et al. [27] used self-etch adhesives after etching but did not compare it without etching. Likewise, Krämer et al. [22] used a universal adhesive after etching but did not compare it without etching. The comparison would have allowed to know if the loss of mineralized tissue by phosphoric acid etching would lead to weaker bonding in hypomineralized enamel.

Chay et al. [18] showed that NaOCl application of etching and before Icon® infiltration significantly enhanced bond strength compared to Icon® without NaOCl. This could be explained by a better penetration of Icon® after the protein removal of MIH-affected enamel. Krämer et al. [22] reported no bond strength increase with the combination of NaOCl and Icon® compared to NaOCl only. However, they did not compare this combination to Icon® only. Nevertheless, Chay et al. [18] tested this comparison and did not observe any significant differences. Thus, the increase of bond strength, compared to no pre-treatment, was more probably due to NaOCl than to Icon®.

**Quality assessment**

Among the 10 studies included, two showed a high risk of bias [25,26], suggesting a global good overall quality. The laboratory studies were especially bad rated on sample size calculation. This can be explained by the difficulty to collect MIH-affected teeth. They also scored poorly on blinding of the tests' operator due for example to the impossibility to blind the adhesive type. On the contrary, all clinical studies were found adequate with the blinding of the outcome assessment. One clinical study did not perform randomization and allocation of patients, and presented uncomplete outcome data [25]. All the others have a few "No" except for patient sample size calculation, which was never done.

**Other leads to explore**

Further studies should focus on the bond strength of other materials to MIH-affected enamel in comparison with composites, such as glass ionomers or compomers. Other studies should investigate the interest of ethanol-wet bonding technique, decreasing the water content, in MIH-affected teeth.

Many studies reported too small samples size, because of the difficulty to collect MIH-affected teeth. It would be beneficial to develop a porous model imitating hypomineralized enamel. Vennat et al. [35] suggested to use deproteinized dentin by heat treatment, because of similar porosity, pore size range and mechanical properties with hypomineralized enamel.

Lastly, more clinical trials should be carried out to confirm the results from laboratory studies.

## **CONCLUSION**

This systematic review emphasizes the need to improve bonding to MIH-affected enamel. Currently, there is very limited evidence of what can solve the issue of adhesion to this tissue. Within the limitation of this review: bond strength of composite to MIH-affected enamel was not significantly different when using self-etch compared to etch-and-rinse adhesives; deproteinization after etching for etch-and-rinse adhesives seemed to enhance bond strength; resin infiltration showed an erratic penetration, however a preliminary deproteinization after etching could improve bond strength; regarding sealants, a study reported no significant differences in retention rate, whereas another recommended to previously apply an adhesive.

These results should be viewed with caution, given the small number of included studies and the variability of MIH severity and the adhesives used.

Further research is needed to achieve improved bonding to MIH-affected enamel.

## **WHY THIS PAPER IS IMPORTANT TO PAEDIATRIC DENTISTS:**

- The prevalence of MIH in young patients is high and it is important to know how best to treat it.
- This systematic review gives all the suggested methods to optimise bonding to MIH-affected enamel.

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**TABLES**

**Table 1: The included laboratory studies: teeth characteristics, materials, bonding protocol, tests and results**

Authors, year	Number of MIH-affected teeth	Number of sound teeth	Severity of hypomineralization	Tooth storage media	Materials used	Bonding protocol	Performed tests	Results
Chay et al. (2013) [18]	84	21	CW (43 teeth), YB (41 teeth)	- 0.02% chlorhexidine (maximum 1 month) - 1% chloramine-T hydrate (2 weeks, room temperature) - rinse in distilled-deionized water, blotted dry, storage in sealed containers with drops of deionized water (2 weeks, room temperature)	- 35% Scotchbond™ Etchant (3M ESPE, St Paul, MN, USA) - Clearfil SE Bond™ (Kuraray Medical Inc., Tokyo, Japan) (Without primer) - Icon®-dry (DMG, Hamburg, Germany) - Icon®-infiltrant (DMG, Hamburg, Germany) - Gradia® Direct (GC Corporation, Tokyo, Japan) - 5.25% NaOCl	- For all gr.: bonding surface involving the ends of enamel prism rods, grounded enamel (600-grits), etching (15s), washing (15s) - Gr. 1 (SE): drying (15s), adhesive (2 coats), air thinning, composite placement - Gr. 2 (HE): drying (15s), adhesive (2 coats), air thinning, composite placement - Gr. 3 (HE+Icon): Icon®-dry (30s), drying (30s), Icon®-infiltrant (3min) + light curing (40 s), Icon®-infiltrant (1min) + light curing (40s), adhesive (1 coat), air thinning, composite placement - Gr. 4 (HE+NaOCl): NaOCl (1min), washing (30s), Icon®-dry (30s), drying (30s), Icon®-infiltrant (3min) + light curing (40 s), Icon®-infiltrant (60s) + light-curing (40s), adhesive (1 coat), air thinning, composite placement	After 12h storage in deionized water at 37°C:  μSBS test + failure mode (LM, SEM)	μSBS: Gr. 1 (SE): 29.0 MPa <sup>a</sup> Gr. 2 (HE): 22.1 MPa <sup>b,c</sup> Gr. 3 (HE+Icon): 19.4 MPa <sup>b</sup> Gr. 4 (HE+NaOCl+Icon): 25.8 MPa <sup>a,c</sup> Gr. 5 (HE+NaOCl): 24.6 MPa <sup>a,c</sup>  μSBS: no significant difference between creamy white and yellow-brown MIH-affected enamel.  Failure mode: - no association between gr. - overall: adhesive 54.3%, mixed 40.0%, cohesive in enamel 4.8% (only for MIH enamel), cohesive failure in

						- Gr. 5 (HE+NaOCl+Icon): NaOCl (1min), washing (30s), Icon®-dry (30s), drying (30s), adhesive (2 coats), air thinning, composite placement.		composite: 7.4%.
Crombie et al. (2013) [19]	19	3	CW (8 teeth), YB (11 teeth)	- 4% neutral buffered formaldehyde (at least 2 weeks) - rinse, storage at 4°C and 100% humidity	- Icon®Caries infiltrant (smooth surfaces) clinical kit: Icon®-etch, Icon®-dry, Icon®-infiltrant (DMG, Hamburg, Germany) - 0.95% NaOCl	- Standard gr.: Icon®according to manufacturer instructions (HCl etching, ethanol, infiltrant resin) - Pretreatment gr.: NaOCl prior etching (2min), water rinsing (2min) - Mid-treatment gr.: NaOCl following etching (2min), water rinsing (2min)	After 24h: - Microhardness test - Tooth sections (LM, SEM).	Microhardness changes: - Standard gr: 0.9 GPa - Pre-treatment: 0.7 GPa -Mid-treatment: 1.3 (or 1.0) GPa  MO examination: significant, but erratic infiltrant resin penetration.
Ekambaram et al. (2017) [20]	27 (one to four specimens per tooth)	0 (30 sound areas from MIH teeth)	CW (15 specimens), YB (15 specimens)	- storage in 0.5% thymol solution at 4°C	- Scotchbond™ Universal Etchant (3M ESPE, St. Paul, MN, USA) - 5% NaOCl (Henan Hairen Biotechnology Co. Ltd, China) - Papacarie Duo® (F&A Pharmaceutical Laboratory Ltd, Sao Paulo, Brazil) - Adper Single Bond 2 (3M ESPE, St. Paul, MN, USA) (TEA) - Filtek™ Z250 universal restorative (3M ESPE, St. Paul, MN, USA)	- For all gr.: grounded enamel (600 grits), etching (10 s), washing (10s), deproteinization if any (60s), washing (10s), drying, adhesive (2 coats) + light curing (10s), composite placement. - Gr. 1 (SE): no deproteinization - Gr. 2 (SE): NaOCl - Gr. 3 (SE): Papacarie gel - Gr. 4 (HE: CW or YB): no deproteinization - Gr. 5 (HE: CW or YB): NaOCl - Gr. 6 (HE: CW or YB): Papacarie gel	After 24h storage at 37°C: μSBS test + failure mode (LM, SEM)	μSBS: Gr.1 (SE): 29.5 MPa <sup>a</sup> Gr. 2 (SE+NaOCl): 27.2 MPa <sup>a</sup> Gr.3 (SE+Papacarie): 27.9 <sup>a</sup> MPa Gr. 4 (HE): 18.64 MPa <sup>b</sup> Gr. 5 (HE+NaOCl): 24.3 MPa <sup>a</sup> Gr. 6 (HE+Papacarie): 24.6 MPa <sup>a</sup>  Deproteinization: bond strength increased for CW specimens, in regards to no treatment. No significant

								increase for YB specimens.  To SE: adhesive failure was the most common, then mixed failure. To HE: cohesive failure in enamel were seen, but reduced by deproteinization.
Gandhi et al. (2012) [21]	31 (divided into three sections each: 93 specimens)	-	-	70% ethanol	- 35% Delton Phosphoric Acid (Dentsply DeTrey GmbH, Konstanz, Germany) - 5% NaOCl - Delton® Light Cure Fissure Sealant (Dentsply DeTrey GmbH, Konstanz, Germany)	- For all gr.: pumicing (bristle brush 60s), washing (30s), drying (30s) - Control gr.: etching (30s), washing (30s), drying (30s), sealant placement (light-curing 20s) - Gr. 1: NaOCl (60s), washing (30s), drying (30s), etching (30s), washing (30s), drying (30s), sealant placement (light-curing 20s) - Gr. 2: NaOCl (60s), washing (30s), drying (30s), sealant placement (light-curing 20s)	After hydrochloric acid (50s), deionized water (60s), freeze drying at -60°C during 24h: - Depth of <i>in vitro</i> enamel infiltration (or the lack of it), i.e. quality of resin tags (SEM)	No significant difference between control gr. and gr. 1: NaOCl have no impact.  Significant difference between control gr. and gr.2: omission of etching seriously compromises the bonding.  Probability of observing weak quality of sealant tags: control gr. 47%, gr.1: 49%, gr. 2: 40%.
Krämer et al. (2017) [22]	35	33	Up to moderate appearance	0.5% chloramine T (maximum 1 month)	- 37,5% phosphoric acid - 5,25% NaOCl - Optibond FL (OFL) (Kerr Dental, Orange, CA, USA) (TEA)	- For all gr.: grounded enamel (180 grits) - Gr. 1 (SE): etching (30s), rinsing (15s), drying, OFL (15s), drying, light-curing (10s) - Gr. 2 (HE): etching (30s), rinsing (15s),	- μTBS test + failure mode (LM, SEM) - Icon® resin infiltration: CLSM	μTBS: Gr. 1 (SE,OFL): 31.2 MPa <sup>a</sup> Gr. 2 (HE,OFL): 21.3 MPa <sup>b</sup> Gr. 3 (HE, NaOCl+OFL): 23.6 MPa <sup>b,c</sup>

					<ul style="list-style-type: none"> <li>- Scotchbond™ Universal adhesive (SU) (3M ESPE, St. Paul, MN, USA) (UA)</li> <li>- Clearfil SE Bond (Cf) (Kuraray Medical Inc, Tokyo, Japan) (SEA)</li> <li>- Z250 (3M Espe, Seefeld, Germany)</li> <li>- Icon® (DMG, Hamburg, Germany)</li> </ul>	<ul style="list-style-type: none"> <li>drying, OFL (15s), drying, light-curing (10s).</li> <li>- Gr. 3 (HE): etching (30s), rinsing (15s), drying, NaOCl (1min), rinsing (30s), OFL (15s), drying, light-curing (10s)</li> <li>- Gr. 4 (HE): Icon®-etch (2min), rinsing (15s), drying, NaOCl (60s), rinsing (30s), Icon®-dry (30s), drying (30s), Icon®-infiltrant (3min) + light-curing (40s), Icon®-infiltrant (1min) + light-curing (40s), OFL (15s), drying, light-curing (10s)</li> <li>- Gr. 5/6 (SE/HE): etching (30s), rinsing (15s), drying, SU (20s), drying (5s), light-curing (10s)</li> <li>- Gr. 7/8 (SE/HE): Cf primer (20s), drying, Cf adhesive, drying, light-curing (10s)</li> </ul>		<ul style="list-style-type: none"> <li>Gr. 4 (HE, NaOCl+Icon+OFL): 24.5 MPa<sup>c</sup></li> <li>Gr. 5 (SE,SU): 34.6 MPa<sup>a</sup></li> <li>Gr. 6 (HE,SU): 16.8 MPa<sup>b,d</sup></li> <li>Gr. 7 (SE,Cf): 24.5 MPa<sup>b,c</sup></li> <li>Gr. 8 (HE,Cf): 11.3 MPa<sup>d</sup></li> </ul> <p>Gr. 3 and 4: NaOCl caused less pre-test failures</p> <p>Gr. 6 and 8 (SE, 2-step SEA and UA): lowest values in HE with most pre-test failures (p &lt; 0.05)</p>
William et al. (2006) [23]	56	44	YB, post-eruption enamel breakdown or failed restoration	<ul style="list-style-type: none"> <li>- 10% neutral buffered formalin at room temperature (maximum 10 months)</li> <li>- specimens stored in 0.5% Chloramine-T</li> </ul>	<ul style="list-style-type: none"> <li>- Scotchbond™ Universal Etchant (3M ESPE, St. Paul, MN, USA)</li> <li>- Single Bond (3M ESPE, St. Paul, Minn) (TEA)</li> <li>- Clearfil SE Bond (Kuraray Medical Inc, Tokyo, Japan) (SEA)</li> <li>- Filtek Supreme Universal Restorative (3M ESPE)</li> </ul>	<ul style="list-style-type: none"> <li>- For all gr.: bonding surface perpendicular to enamel rods, grounded enamel (600 grits)</li> <li>- gr. SE/HE: single bond following manufacturers' instructions, composite placement</li> <li>- gr. SE/HE: clearfil SE Bond following manufacturers' instructions, composite placement</li> </ul>	<ul style="list-style-type: none"> <li>After 12h at 37°C:</li> <li>- μSBS test + failure mode (LM, SEM)</li> <li>- Etch pattern and interface observations: SEM</li> </ul>	<ul style="list-style-type: none"> <li>μSBS:</li> <li>- SE, SB: 16.3 MPa<sup>a</sup></li> <li>- SE, CfB: 19.6 MPa<sup>a</sup></li> <li>- HE, SB: 7.1 MPa<sup>b</sup></li> <li>- HE, CfB: 10.4 MPa<sup>b</sup></li> </ul> <p>Failure modes:</p> <ul style="list-style-type: none"> <li>- significant difference between SE (predominantly adhesive or mixed) and HE (predominantly cohesive in</li> </ul>



								<p>enamel)</p> <ul style="list-style-type: none"><li>- No association between failure modes and adhesive type (enamel cohesive failures: TE: 50%, SE 52%; mixed failures TE 14%, SE 13%)</li></ul> <p>SEM images of etch enamel:</p> <ul style="list-style-type: none"><li>- with Scotchbond etchant:<ul style="list-style-type: none"><li>&gt; section perpendicular to enamel rods: for SE, preferential inter-rod enamel dissolution and intercrystal porosity; for HE, preferential inter-rod dissolution and poor intercrystal porosity</li><li>&gt; section parallel to enamel rods: for SE, preferential inter-rod enamel dissolution; for HE, poor enamel etching with little preferential removal of inter-rod enamel.</li></ul></li><li>- With Clearfil SE Bond Primer:<ul style="list-style-type: none"><li>&gt; section perpendicular to enamel rods: for SE,</li></ul></li></ul>
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**Table 2: The included clinical studies, study design, teeth characteristics, materials, bonding protocol, follow-up and results**

Authors, year	Study design	Number of patients (age range)	Number of MIH teeth	Control gr.	Severity of hypomineralization	Materials used	Bonding protocol	Follow-up	Results
De Souza et al. 2017 [24]	Prospective, randomized, single-blind clinical trial. One experienced operator performed the composites. Examiners' calibration for: MIH, DMFT index, USPHS-modified evaluation.	18 children (6-8 years)	41 (22 for TEA, 19 for SEA)	MIH teeth treated with TEA. (No teeth with sound enamel)	Severe: MIH with posteruptive enamel breakdown, caries lesions, and opacities associated with atypical restorations	<ul style="list-style-type: none"> <li>- Duraphat, (Colgate Palmolive, New York, USA)</li> <li>- Ketac Molar Easymix (3M ESPE, St Paul, MN, USA)</li> <li>- 35% phosphoric acid (3M ESPE, St Paul, MN, USA)</li> <li>- Adper Scotchbond Multi-Purpose (3M ESPE, St Paul, MN, USA) (TEA)</li> <li>- Clearfil SE Bond (Kuraray Medical, Tokyo, Japan) (SEA)</li> <li>- Filtek XT350 (3M ESPE, St Paul, MN, USA)</li> <li>- Fluoride gel application</li> </ul>	<ul style="list-style-type: none"> <li>- Fluoride: 1 month of weekly varnish application</li> <li>- Provisional restoration: caries removal under rubber dam, chlorhexidine (1%), Ca(OH)<sub>2</sub> if necessary, GIC. (+dietary and hygiene instructions).</li> <li>- Two months after, partial removal of GIC (prophylaxis, rubber dam):</li> </ul> <p>Gr. 1 (TEA): etching (30s), washing, drying (5s), primer (5s), drying, adhesive (5s), light-curing (20s)</p> <p>Gr. 2 (SEA): primer (20s), drying (5s), adhesive (5s), light-curing (10 s).</p>	Permanent restoration monitored at 1, 6, 12, and 18 months. (100% overall recall rate) Each visit: dietary and hygiene instruction, fluoride gel application 5% NaF, if indicated. Success rate: evaluation by USPHS-modified criteria.	Success rate (18 months): Gr.1 (TEA): 54% Gr. 2 (SEA): 68% not significantly different (except more failure for upper teeth in gr. 2)

						5% NaF (FGM, Joinville, SC, Brazil).	- Composite placement in increments (40s) - Each 6 month, if necessary: dietary and oral hygiene instructions, teeth cleaning, and fluoride gel application		
Fragelli et al. 2017 [25]	Prospective, single-blind clinical trial. One experienced operator performed the sealants. Examiners' calibration for: MIH and USPHS-modified criteria evaluation.	21 children (6-7 years)	25	16 sound teeth	Mild: white, yellow, and brown opacities with high risk for carious lesion or breakdown	- Duraphat, (Colgate-Palmolive, New York, USA) - Scotchbond™ universal etchant (3M/ESPE, St. Paul, USA) - FluroShield, (Dentsply/Caulk, Milford, DE, USA)	Fluoride: 1 month of weekly varnish application. - Gr. 1: SE - Gr. 2: HE Rubber dam, etching (30s), rinsing, drying (5s), resin sealant, light curing (20s)	18 months follow-up. (72.4% overall recall rate) Success rate: evaluation by USPHS criteria	Unchanged sealants at 18 months: -SE: 62%, HE: 72% not significantly different - 16 and 26: more failure in both groups - No significant difference according to the MIH colour. - Failures in gr. HE: frequently retention loss, secondary caries, marginal adaptation and discoloration.
Lygidakis et al.	Prospective, randomized,	47 children	94	MIH teeth treated	Mild defect: demarcated	- 35% orthophosphoric acid - One-step® (Bisco, Inc.,	For all groups: fissure cleaning with bristle brush and non-	Evaluation at 48 months	After 4 years: Gr. 1: 70% fully

2009 [26]	single-blind clinical trial (a split-mouth experimental design). One experienced operator implemented the sealants. Evaluation by one blind examiner.	(6-7 years)		without adhesive.	opacities, without breakdown.	Schaumburg, USA) - Fissurit® (Voco GmbH, Cuxhaven, Germany)	fluoridated paste, cotton roll isolation. Gr. 1: etching (30s), washing (15s), drying (10s), adhesive (2 coats), light-curing, sealant placement, light-curing (30 s). Gr. 2: etching (30s), washing (15s), drying (10s), sealant placement, light-curing (30 s).	(87% overall recall rate). Success rate: sealant retention evaluation	sealed, 30% partly. Gr. 2: 26% fully sealed, 45% partly sealed, 30% unsealed. Sealant retention on MIH-affected molar: significant increase when using 1-step TEA after etching.
Sönmez et al. 2017 [27]	Prospective, randomized, single-blind clinical trial. One operator performed the cavity preparations and the composites. Examiners'	30 patients (8-12)	95	31 sound teeth	Severe: cream or yellowish enamel, with atypical cavities and post-eruptive breakdown associated with dental caries, requiring 2 surfaced	- ETCH-37TM (Bisco, Inc., Schaumburg, USA) - 5% NaOCl - Futurabond NR, (VOCO, Inc. USA) (SEA) - Grandio (VOCO, Inc., USA)	Cavity design: Invasive: margins in sound enamel. Non-invasive: margins removed until the bur met with significant resistance from the hypomineralized enamel. - All groups: rubber dam - Gr. 1 (invasive): etching (20s), rinsing (15s), drying, SEA, composite placement	Every 3 months for 24 months. (100% overall recall rate) Success rate: evaluation by USPHS criteria.	No significant difference until 12 months.  Success rate (2 years): 24 months: Gr. 1: 81.25% <sup>a</sup> Gr. 2: 58.6% <sup>b</sup> Gr. 3: 78.12% <sup>a</sup> Gr. 4: 87.09 % <sup>a</sup>

calibration for: MIH and USPHS- modified criteria evaluation.					restorations.		<p>- Gr. 2 (non-invasive): etching (20s), rinsing (15s), drying, SEA, composite placement</p> <p>- Gr. 3 (non-invasive): etching (20s), NaOCl (1min), rinsing (15s), drying, SEA, composite placement</p> <p>- Gr. 4 (SE): etching (20s), rinsing (15s), drying, SEA, composite placement</p>		Failures in anatomic form, marginal adaptation and marginal discoloration: significant increase after 12 months in gr.2, after 18 months in gr. 1 and 3. No difference in gr. 4.
Abbreviations: gr: group, SE: sound enamel, HE: hypomineralized enamel; CW: creamy-white; YB: yellow-brown; TEA: total-etch adhesive; SEA: self-etch adhesive; UA: universal adhesive; GIC: glass ionomer cement.									
For each article (independently): same subscript letters indicate no significant difference.									

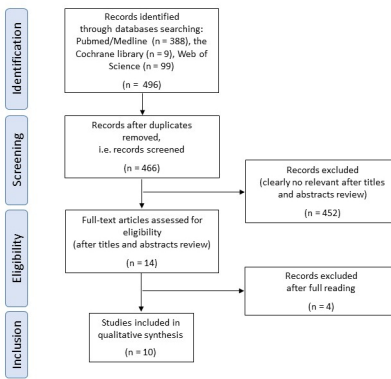
## FIGURE LEGENDS

Fig. 1: Flowchart describing the search strategy.

Fig. 2a and 2b: Risk of bias graph: authors' assessment of each risk of bias item in proportions, respectively for all laboratory and clinical studies.

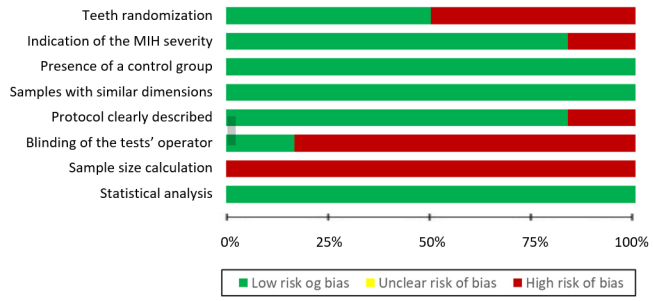
Fig. 3: Risk of bias summary: authors' assessment of each risk of bias item, for each included laboratory study.

Fig. 4: Risk of bias summary: authors' assessment of each risk of bias item, for each included clinical study.

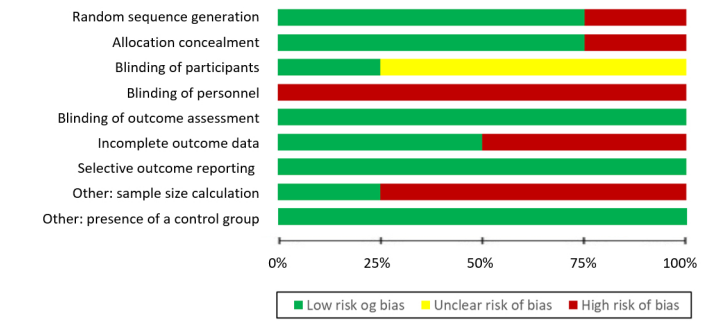


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	Teeth randomization	Indication of the MIH severity	Presence of a control group	Samples with similar dimensions	Protocol clearly described	Blinding of the tests' operator	Sample size calculation	Statistical analysis
Chay 2013	-	+	+	+	+	-	-	+
Crombie 2013	-	+	+	+	+	-	-	+
Ekambaram 2017	+	+	+	+	+	-	-	+
Gandhi 2012	+	-	+	+	+	+	-	+
Krämer 2017	+	+	+	+	-	-	-	+
Williams 2006	-	+	+	+	+	-	-	+

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	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other: sample size calculation	Other: presence of a control group
De Souza 2017	+	+	+	-	+	+	+	-	+
Fragelli 2017	-	-	?	-	+	-	+	+	+
Lygidakis 2009	+	+	?	-	+	-	+	-	+
Sönmez 2017	+	+	?	-	+	+	+	-	+

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