SYSTEMATIC REVIEW O

# A Qualitative Analysis of Treatment Patterns for Mild and Severe Molar Hypomineralization in Permanent Teeth: A Systematic Review

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**Abstract:** ***Purpose:*** *Using a systematic review to answer the following question: What are the treatment patterns for mild and severe molar hypomineralization in permanent teeth?* ***Methods:*** *Electronic searches were conducted to identify randomized clinical trials (RCT) that related treatment to molar hypomineralization- (MH) affected permanent molars in children from five to 16 years old. Data extraction and risk of bias evaluation, using the Cochrane risk of bias tool, were performed for all included studies. Studies were selected according to PICOS criteria. RCTs relating mild and severe MH to treatments on permanent molars were included. Studies analyzing clinical techniques, whether single or any association of techniques for restorative and desensitizing treatments, were included. Studies involving another disease or comparing different types of enamel defects related to trauma and hereditary were excluded. The certainty of the evidence was evaluated using the GRADE approach.* ***Results:*** *The electronic search was performed on MEDLINE via PubMed, Embase, Cochrane Library, and Grey literature up to May 9, 2022. Of the 5,201 studies initially identified, 88 were fully assessed and 14 RCTs were included. A total of 2,399 interventions were analyzed in 576 patients. Certainty of evidence was found to be of low quality for the outcomes remineralization, structural integrity maintenance, and decay prevention, and very low quality for hypersensitivity decrease and retention.* ***Conclusions:*** *Mild molar hypomineralization needs remineralization, desensitization, sealants, and close follow-up. Severe MH requires restoration both to treat hypersensitivity and reconstruct the affected teeth. Yellow-brown defects have a poor prognosis.* *(Pediatr Dent 2023;45(4):281-91) Received October 30, 2022 | Last Revision February 9, 2023 | Accepted February 10, 2023*

KEYWORDS: MOLAR HYPOMINERALIZATION; MH TREATMENT; PERMANENT TEETH; SYSTEMATIC REVIEW

In 2001, Weerheijm et al.[1] defined molar incisor hypomineralization (**MIH**) as a specific disease characterized by hypomineralization of systemic origin of one to four permanent molars, and frequently affecting incisors, differentiating it from other types of enamel defects. Since then, studies have become more focused on trying to better define and relate etiology, diagnosis, prevalence, and treatment.[2,3]

The estimated global prevalence reported for MIH is around 13 percent.[2] The etiology is multifactorial and thought to be the result of systemic environmental factors during the first three years of life that affect enamel development during the pre-, peri-, or early post-natal phases of life.[1,4,5] Vieira and Manton[6] suggested that genetics can contribute to the development of MIH,[6] while Lopes et al.[2] reported that high amounts of proteins–such as serum albumin, type I collagen, and others–inhibit the growth of hydroxyapatite crystals and enzymatic activity on the maturation phase, reducing the mineral content of enamel.[2] Despite the presence of many studies and theories investigating potential factors involved in the occurrence of MIH, the results are still inconclusive.[3]

The great variability of clinical findings, including the extent of enamel breakdown, enamel coloration, and symptomatology, are factors that further complicate diagnosis and treatment plans.[2,7] Thus, a classification that can relate treatment with diagnosis is quite important to guide the clinicians in the sense that the treatment approach will directly depend on the extent of the lesion. MIH-affected teeth are classified as mild when there are demarcated opacities without posteruptive enamel breakdown (**PEB**) and severe when PEB occurs.[8,9]

The most common diagnostic finding is the presence of affected molars by age six years, but primary and permanent second molars can also be affected alone or together, as well as primary and permanent incisors. The latter present slightly different characteristics, without a predisposition to enamel fractures and sensitivity when compared to molars.[7]

Molar hypomineralization (**MH**) is clinically defined by demarcated enamel opacities that can manifest as white, cream, yellow, or brown defects and are sharply demarcated against normal enamel.[7] Histologically, these affected areas have fewer distinct prism sheets and a lack of arrangement of the enamel crystals.[10] The molar defect appears to extend gingivally from cuspal tips but rarely involves the cervical enamel, and the demarcated opacities may possess decreased mechanical properties such as hardness and modulus of elasticity[11] as well as increased roughness and porosity compared to normal enamel. The enamel shears off under masticatory force and can result in PEB. Because of that, these affected teeth are more prone to enamel breakdown and the development of carious lesions, sensitivity, and, consequently, an earlier and more frequent need for dental treatment.[4]

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**HOW TO CITE:**

Ritto FP, Tiwana KR, Schmitz TA, Dacus ZL, Borges MAP, Canellas JV. A qualitative analysis of treatment patterns for mild and severe molar hypomineralization in permanent teeth: A systematic review. Pediatr Dent 2023;45(4):281-91.

Treatment options are diverse, and management of MH is challenging due to the different presentations of the disease combined with a broad spectrum of treatment modalities: prevention and management of hypersensitivity, direct and indirect restorations, and extractions.[8] However, because of the different severities of the disease, it's difficult to establish the line of treatment to be followed.

Therefore, it is recognized that MH is a clinical concern worldwide and more guidance is needed in terms of treatments and protocols as well as more clinical research evidence on how to properly treat each level of this disease to achieve the best results in terms of clinical longevity and patient acceptance and satisfaction.[12]

This study's purpose was to perform a systematic review to answer the focused question: What are the treatment patterns for mild and severe molar hypomineralization in permanent teeth? There is no previous systematic review comparing randomized clinical trials (**RCTs**) that relate the different severity of MH to a specific treatment.

## Methods

**PICOS strategy and eligibility criteria.** This systematic review was presented according to the PRISMA 2020.[13] The PICOS strategy (Patient, Intervention, Comparison, Outcome, and Study) was used to formulate a well-designed question.

**Research protocol.** The protocol was registered prospectively in the Platform of Registered Systematic Review and Metaanalysis Protocols INPLASY (registration number INPLASY202230127).

The study compared the outcomes of specific treatments for mild and severe MH. Eligible studies were RCTs that included children from five to 16 years old, with no restrictions regarding sex or ethnicity. Only studies analyzing clinical techniques, whether single techniques or any association of techniques for restorative and desensitizing treatments in affected permanent molars, were included. Studies involving another disease or comparing different types of enamel defects related to trauma and hereditary, like fluorosis or amelogenesis imperfecta, were excluded. Finally, studies for treatment in primary dentition were excluded.

**Literature search.** Identification of studies was conducted through a detailed search strategy on Embase, MEDLINE via PubMed®, and Cochrane Central Register of Controlled trial (via Ovid) up to May 9, 2022. Medical subject heading terms (**MeSh**) and free-text words were used on the electronic database searches as follows:

1. Embase (Molar Incisor Hypomineralization OR MIH OR Dental Enamel Hypoplasia (MeSh) OR Tooth demineralization/therapy (MeSh) (((((((((Randomized controlled trial [Publication Type]) OR controlled clinical trial [Publication Type]) OR randomized [Title/Abstract]) OR placebo [Title/Abstract]) OR randomly [Title/Abstract]) OR trial [Title])) OR "Clinical Trials as Topic"[MeSh:NoExp])) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms.
2. Cochrane Central Register of Controlled Trials (via Ovid): ((molar incisor hypomineral*.mp. OR mih.mp. OR dental enamel hypopla*.mp. OR ((tooth or teeth or dental or enamel) adj3 demineral*).mp.) AND (randomized controlled trial.pt. OR controlled clinical trial.pt. OR random*. ti, ab, kw. OR placebo. ti,ab,kw. OR trial. ti. OR clinical trials as topic/)) NOT (exp Animals/ NOT exp Humans/).
3. MEDLINE via PubMed (Molar Incisor Hypomineralization OR MIH OR Dental Enamel Hypoplasia (MeSh) OR Tooth demineralization/therapy (MeSh) (((((((((Randomized controlled trial [Publication Type]) OR controlled clinical trial [Publication Type]) OR randomized [Title/Abstract]) OR placebo [Title/Abstract]) OR randomly [Title/Abstract]) OR trial [Title])) OR "Clinical Trials as Topic"[MeSh:NoExp])) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms.

No restrictions on country, publication status, setting, or language were applied. Additionally, the reference lists of the included studies were cross-checked to identify relevant studies. Grey literature was screened through ClinicalTrials.gov. Furthermore, a comprehensive manual search was conducted in the following journals: European Journal of Paediatric Dentistry; International Journal of Paediatric Dentistry; Pediatric Dentistry; Caries Research; Dental Materials; and Operative Dentistry. Also, Science Direct and Google academics were used for the manual search and the articles were imported into Endnote 20 (Thompson Reuters, Philadelphia, Pa., USA), where duplicates were removed.

**Study selection.** All searched titles, abstracts, and full-text articles were independently reviewed by two investigators. For measurement reproducibility purposes and inter-examiner reliability, kappa statistics were used. Any disagreement over inclusion or inclusion criteria was resolved by discussion with a third author.

**Data extraction and analysis.** To arrive at the results, the studies were first divided into two groups: groups analyzing mild MH (Table 1) and groups analyzing severe MH (Table 2).

The classification terms "mild" and "severe" were extracted from the sub-section called "severity of the defects" within the section entitled "terminology and diagnosis of MIH" of the updated European Academy of Paediatric Dentistry policy document.[9] The document reinforces the use of this classification to clarify the diagnosis and formulate an appropriate treatment plan. The main characteristic of the classification used to differentiate the groups was the absence or the presence of PEB.

In each table, the following characteristics of the selected studies were gathered: author; publication year; country; age range; the sample size of patients and teeth; type of teeth; monitoring time; groups tested; diagnosis criteria; intervention; material; type of measurements; results; outcomes; where failures prevailed; and authors suggestion for improving results. The corresponding author was contacted when data were missing. The treatments at each stage were compared separately and within each table, and a qualitative analysis was performed in subgroups according to the outcomes evaluated in the clinical study (remineralization, structural integrity, hypersensitivity decrease, decay prevention, and material retention).

**Quality appraisal.** The Cochrane Collaboration tool was used for assessing the risk of bias in included studies. Two review authors independently assessed the risk of bias. The reviewers were blinded to information about the articles. The assessment of the risk of bias was undertaken as follows: low risk of bias when all the domains were judged to be at low risk of bias; unclear risk of bias when one or more domains were judged to be at unclear risk of bias; and high risk of bias when one or more domains were judged to be at high risk of bias.

Table 1. INCLUDED STUDIES INVOLVING MILD MOLAR INCISOR HYPOMINERALIZATION AND NO POSTERUPTIVE ENAMEL BREAKDOWN*

| Reference | Age range (years) | Children/ treated type of teeth | Monitoring time | Groups tested | Diagnosis criteria | Treatment (intervention/material) |
|---|---|---|---|---|---|---|
| Bekes et al. 2022 Germany/ Austria | 6-10 | 38 children 76 PFM | 12 weeks (1, 4, 8, 12 weeks) | 1. Scotchbond universal (adhesive) + Clinpro sealant (light cure resin-based sealant)<br>2. Ketac Universal (glass ionomer cement) | Evaluate retention of material and restoration survival (USPHS), dental pain (SCASS/WBFS) and caries prevention | Resin-based sealants and glass ionomer-based sealants (GI sealants) |
| Olgen et al. 2021 Turkey | 6-9 | 49 children 90 PFM | 24 months (3, 6, 9, 12, 15, 18, 21, 24) | 1. Fluoride varnish 5% NaF (4x/week; Duraphat)- 6 months/6 months<br>2. CPP-ACP (2x/day for 3 months) – Tooth mousse GC<br>3. CPP-ACFP<br>4. No treatment, only hygiene oral training | Evaluate the maintaining of structural integrity, remineralization and caries prevention | 5% NaF and CPP-ACP |
| Nogueira et al. 2021 Brazil | 6-12 | 51 children 135 PFM and 100 incisors | 18 months (1, 3, 6, 12, 18 months) | 1. Application of 5% NaF fluoride (4x/week)<br>2. Etch 37% phosphoric acid + 5% NaF (4x/week)<br>3. Resin infiltration (Icon) – 1 application | If the procedure maintains the structural integrity of teeth | Fluoride varnish therapy 5% NaF (Duraphat) and Icon infiltrant |
| Prathima et al. 2021 India | 8-10 | 32 children | No 15/30 minutes to measure | 1. Chewing gum CPP-ACP (test group)<br>2. Chewing gum containing xylitol (control group) | Evaluate the salivary characteristics related to remineralization | Gum with CPP-ACP and gum with xylitol |
| Ballikaya et al. 2021 Turkey | 6-13 | 48 children 112 PFM | 12 months (1, 6, 12 months) | 1. SDF application (Riva Star 30-35% SDF + KI saturated solution)<br>2. SDF (Riva Star)+ART with HVGIC (Equia Forte GC) | Evaluate structural integrity (enamel breakdown), dental pain (hypersensitivity), and formation of caries | SDF and sealants (high viscosity glass ionomer by ATR technique) |
| Schraverus et al. 2021 Amsterdam/ Mexico | 5- 9 | 77 children 228 PFM | 12 months (6, 12 months) | 1. No treatment (control group)<br>2. GIC conditioner + glass ionomer sealant (Fuji Triage Pink) | If the GIC sealant has any preventive effect on structural integrity regarding caries and enamel PEB | Glass ionomer cement (Fuji Triage Pink) |
| Muniz et al. 2020 Brazil | 6-12 | 66 children 102 PFM and 112 incisors | 1 month | 1. Laser (low-level laser diode) – 2 sessions<br>2. Fluoride varnish (4 x/week)<br>3. Laser+fluoride varnish –2 sessions laser 4 x/week fluoride varnish (Duraphat 22,600 ppm) | Evaluate the efficiency of the association of laser and varnish for dental pain (desensitization) | Lower power laser+fluoride varnish (5% NaF Duraphat) |
| Restrepo et al. 2016 Brazil | 9-12 | 51 children 107 PFM and 51 incisors | 4 weeks (1 month) | 1. Application of 5% NaF fluoride (4x/week)<br>2. No treatment | If there was or was not remineralization and structural integrity maintenance | Fluoride varnish therapy 5% NaF (Duraphat) |
| Lygidakis et al. 2009 Greece | 6-11 | 47 children 47 PFM | 48 months | 1. 37% acid phosphoric etch + Bisco One-Step (prime+bond) + sealant (Fissurit-Voco)<br>2. 37% acid phosphoric etch + sealants– etch and seal | Evaluate the survival of sealants | Etch and seal technique and add fifth-generation prime/adhesive (Bisco One-Step) |
| Ehlers et al. 2021 Germany mild and severe MIH | 6-16 | 21 children/ 48 molars | 2 months (1, 2 months) | 1. Toothpaste (10% microcrystalline hydroxyapatite) – Kinder Karex<br>2. Toothpaste (amine fluoride 1,400 ppm fluoride) – Elmex Junior | Dental pain (hypersensitivity) – SCASS/WBFS (tactile and air blast stimuli) | Toothpaste with hydroxyapatite and fluoride |

*Table continued on the next page.*

* Abbreviations used in this table: ART=atraumatic restorative treatment; CPP-ACFP=casein phosphopeptide amorphous calcium fluoride phosphate; CPP-ACP= casein phosphopeptide-amorphous calcium phosphate; KI=saturated solution of Potassium Iodide; HVGIC=high viscosity glass ionomer cement; MIH=molar incisor hypomineralization; PEB=posteruptive enamel breakdown; PFM=permanent first molars; NaF=sodium fluoride; SDF=silver diamine fluoride; SCASS= Schiff Cold Air Sensitivity Scale[23,27]; WBFS=Wong Baker Faces Scale[43]; USPHS=United States Public Health Service criteria[27,29].

Table 1. CONTINUED*

| Reference | Type of measurements | Results | Outcome / difference between groups | Where failures prevailed | Author suggestion for improving results |
|---|---|---|---|---|---|
| Bekes et al. 2022 Germany/ Austria | **Restoration survival and retention of sealant:** USPHS criteria **Hypersensitivity** was measured by SCASS and WBFS | Resin and GI sealants were able to reduce hypersensitivity successfully immediately and throughout 12 weeks both materials performed similar in terms of retention | Restoration survival (sealant / retention): yes diminish hypersensitivity: yes | Not mentioned | Author suggested larger sample |
| Olgen et al. 2021 Turkey | **Enamel integrity (Development of PEB)** were evaluated clinically and visually. **Remineralization** was measured with laser Fluorescence method (Diagnodent) | Remineralization: was found in groups 2 and 3, remineralization on 3 was faster, even in tooth with yellow-brown defects. Structural integrity: control group (4) proved less successful than the other groups no difference was found between groups | Had remineralization (Diagnodent): yes for 1, 2 <3 (2,3 faster) no for 4; maintain structural integrity: yes 1, 2, 3 no for 4 prevent caries: yes for 2, 3 no for 1 (in the fissures), 4, especially in teeth with YB defects | Yellow-brown defects of the groups 1 and 4 | Comparative clinical studies are needed |
| Nogueira et al. 2021 Brazil | **Enamel integrity** on **pictures** measured by visualization and clinical evaluation | Fluoride therapy and resin infiltration had different results on maintaining enamel integrity. Icon positively influenced the structural integrity on incisors | Maintain structural integrity/development of PEB: no for varnish/ yes for infiltrant | Failures prevailed in molars (3.5 times more than incisors) | Not mentioned |
| Prathima et al. 2021 India | Salivary PH, flow rate and buffering action | Both groups improved the salivary properties | No difference between groups | Not mentioned | Not mentioned |
| Ballikaya et al. 2021 Turkey | **Restoration survival** (cumulative survival rates) **enamel integrity (enamel breakdown) and caries** were evaluated by clinical exam and pictures evaluation **hypersensitivity** was measured by SCASS | Glass ionomer placed after SDF showed a reasonable retention rate, marginal discoloration from SDF was a side effect, hypersensitivity showed lower scores at all evaluation periods. No difference for hypersensitivity was found between groups | Restoration survival (sealant/retention): yes maintain structural integrity: yes diminish hypersensitivity: yes | Failures on restoration prevailed on palatal surfaces of the molars and on the yellow-brown defects | Color, size, and location of hypomineralized lesions showed variations. Future clinical trials should standardize the lesions. |
| Schraverus et al. 2021 Amsterdam/ Mexico | **Clinical exam** and **pictures** evaluation. | Glass ionomer sealants can prevent dental caries but cannot prevent post-eruptive enamel breakdown | Patient anxiety was reduced: yes (no difference) enamel breakdown was reduced: no (no difference) caries was reduced: yes | Teeth with yellow-brown opacities were 5 times more likely to have PEB, atypical restoration, atypical caries, or extraction due to MIH. Sealed molars present 77% less chance of caries than unsealed. | Further studies are needed to establish if PEB leads to caries development or caries is a contributing factor for PEB |
| Muniz et al. 2020 Brazil | Scale for the assessment of **pain intensity** | Fluoride Varnish and the combination (laser + Fluoride Varnish) had greater desensitizing action. Laser demonstrated an immediate desensitizing effect and fluoride varnish had a late onset effect. | Dental pain was reduced: yes (FV+L group was more effective) | 1st Molars exhibited greater sensitivity. Molars exhibited significantly greater sensitivity than incisors (enamel is thinner on incisors, but the severity of the defects are higher on molars). | Further studies should be conducted to evaluate the duration of the desensitizing action of the treatment used herein |
| Restrepo et al. 2016 Brazil | **Remineralization** and **enamel integrity (development of PEB)** on pictures measured with quantitative light-induced fluorescence | No difference between groups for both | Had remineralization: no (no difference) maintain structural integrity: yes (no difference) | 1-maxillary first molars / 2-mandibular first molars/ 3-maxillary central incisor/ 4-mandibular ventral incisor | Increase time of follow-up |
| Lygidakis et al. 2009 Greece | **Restoration survival and retention of sealant:** clinical exam | The use of the 5th generation prime and bond single bottle can improve sealant retention in non-cavitated MIH teeth. | Restoration survival (sealant/ retention): yes group 1 had better results than group 2 with no adhesive | Not mentioned | Long follow-up to define the supremacy of one technique over the other |
| Ehlers et al. 2021 Germany mild and severe MIH | **Hypersensitivity** was measured by SCASS and WBFS | Both toothpastes (hydroxyapatite versus amine fluoride) were effective in relieving hypersensitivity and maintaining desensitization for 8 weeks. Children in the hydroxyapatite group tended to show fewer symptoms. | Diminish hypersensitivity: yes | Girls had more hypersensitivity than boys MIH itself equally affects boys and girls | Larger sample sizes and longer follow-up |

* Abbreviations used in this table: ART=atraumatic restorative treatment; CPP-ACFP=casein phosphopeptide amorphous calcium fluoride phosphate; CPP-ACP=casein phosphopeptide-amorphous calcium phosphate; FV=fluoride varnish; KI=saturated solution of Potassium Iodide; HVGIC=high viscosity glass ionomer cement; L=laser; MIH=molar incisor hypomineralization; PEB=posteruptive enamel breakdown; PFM=permanent first molars; NaF=sodium fluoride; SDF=silver diamine fluoride; SCASS=Schiff Cold Air Sensitivity Scale [23,27]; USPHS=United States Public Health Service criteria[27,29]; WBFS=Wong Baker Faces Scale[43]; YB=Yellow-brow.

**Level of evidence.** The certainty of evidence (certainty in the estimates of effect) was determined using the Grading of Recommendations Assessment, Development, and Evaluation (**GRADE**) approach.[14,15] To evaluate the certainty of evidence among the studies, the GRADE tool[14] was applied, evaluating the following outcomes: remineralization; structural integrity maintenance; hypersensitivity decrease; decay prevention; and retention. Since all the included studies were RCTs, the initial rating of "high" was assigned, which was downgraded by one or two levels if serious or very serious concerns, respectively, were presented in the studies. The included studies were evaluated according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

## Results

The flow diagram of the screening and selection process is presented in Figure 1. Initially, 5,201 potential studies were identified. Of these, 4,875 studies were retained after excluding duplicates. Then, titles and abstracts were screened, eliminating 4,787 studies, resulting in 88 studies. The agreement for the inclusion of studies was considered excellent (Kappa coefficient equals 0.92). After a full-text reading, 14 RCTs[16-29] fulfilled the inclusion criteria and were divided into two groups for qualitative analysis. A total of 2,399 interventions were analyzed for mild and severe MH in 576 patients. A parallel-group design was utilized in all included RCTs. Due to the low number of studies and the high methodological heterogeneity, the outcomes were not subjected to network meta-analyses. Tables 1 and 2 summarize the information of the articles selected. One study[21] compared mild and severe together and was placed in Table 1 for comparison.

Results for mild and severe MH were presented and analyzed separately for better comparison and understanding of the outcomes (remineralization, structural integrity maintenance, hypersensitivity decrease, decay prevention, and retention).

The risk of bias analysis showed that five trials were considered at unclear risk of bias.[16,17,20,23,26] Another nine trials were judged as having a high risk of bias[18,19,21,22,24,25,27-29] because one or more domains were considered high risk of bias (Figure 2).

The certainty of evidence showed that remineralization, structural integrity maintenance, and decay prevention were classified as having a low certainty of evidence, while hypersensitivity and retention were classified as having a very low certainty of evidence (Table 3). All outcomes were downgraded due to the risk of bias, and four of them (structural integrity maintenance, hypersensitivity decrease, decay prevention, and retention) were downgraded for indirectness, with retention being downgraded in two levels due to interventions and comparators. Two outcomes (remineralization and hypersensitivity decrease) were downgraded in one level for imprecision due to the limited amount of data.

**Interpretation of results: Mild MH.** Remineralization was measured in two[17,28] studies evaluating 197 MH-affected molars. Even though five percent sodium fluoride varnish (**NaF**)

Table 2. INCLUDED STUDIES ABOUT SEVERE MOLAR INCISOR HYPOMINERALIZATION WITH POSTERUPTIVE ENAMEL BREAKDOWN*

| Authors/ year | Age range (years) | Children/ treated type of teeth | Monitoring time | Groups tested | Diagnosis criteria | Treatment (intervention/ material) | Type of measurements |
|---|---|---|---|---|---|---|---|
| Rolim et al. 2021 Brazil | 7-17 | 35 children 64 PFM | 12 months | 1. Total-etch- 37% acid phosphoric etch+universal adhesive (Ambar-FGM) + bulk fill composite resin (Tetric). 2. Self-etch (adhesive + composite Ambar/Tetric). | Evaluate the survival of the direct restorations on PFM with MIH/ dental pain/anxiety | Total-etch (TE–37% acid phosphoric etch) and self-etch (SE–no prior etching) in composite restoration | Clinical exam (retention, anatomic form, superficial texture, margin coloring and marginal decay, marginal integrity) and USPHS-modified criteria |
| Singh et al. 2021 India | 8-15 | 46 children 60 PFM | 24 months (6, 12, 24 months) | 1. Lithium disilicate 2. Zirconia 3. Full-cast metal crown | Evaluate and compare (retention, marginal adaption, desensitization, proximal contact, gingival health) (USPHS criteria) | Lithium disilicate Zirconia full cast metal crown (All: resin cement for cementation) | Clinical exam/post-sensitivity measurement (USPHS criteria) |
| Dhareula et al. 2019 India | 8-13 | 30 children 42 PFM | 36 months | 1. Cast metal onlay 2. Indirect composite onlay | Evaluate the efficacy of the restorations and compare the retention of them (esthetic versus non-esthetic indirect) | Cast metal and indirect composite | Clinical and radiographic evaluation at 9, 18, and 36 months (USPHS criteria) |
| de Souza et al. 2017 Brazil | 6-8 | 18 children 41 PFM | 18 months | 1. Self-etch adhesive–Clearfill SE bond) + composite resin restoration (Filtek XT 350). 2. Total-etch technique) 37% acid etch + adhesive (Adper Scothbond multipurpose) + composite resin restoration (Filtek XT 350). | Evaluate the survival of the direct restorations on PFM with MIH | Self-etch composite technique and total-etch composite technique | Marginal decay, marginal integrity (USPHS modified criteria) |

*Table continued on the next page.*

* Abbreviations used in this table: MIH=molar incisor hypomineralization; PEB=posteruptive enamel breakdown; PFM=permanent first molars; USPHS=United States Public Health Service criteria[27,29].

Table 2. CONTINUED*

| Authors/ year | Results | Outcome/difference between groups | Where failures prevailed | Author's conclusion | Author suggestion for improving results |
|---|---|---|---|---|---|
| Rolim et al. 2021 Brazil | Restorative protocols presented similar longevity reducing dental pain and patient anxiety | Restoration survival: yes (no difference) dental pain was reduced: yes (no difference) | Restorations with cusp involvement had lower median survival time than did restoration without cusp involvement | Reduction of pain was observed earlier in Self-Etch than in Total-Etch both treatments managed to reduce pain and anxiety | Address not only the clinical outcomes but also patient-centered outcomes. research to check if caries is a contributing factor for Post Eruptive Breakdown |
| Singh et al. 2021 India | No difference between groups, similar success rate | Restoration survival: yes (no difference) hypersensitivity got eliminated post-cementation in 100% | not mentioned | All three types of crowns showed excellent retention over 24 months. Complete resolution of hypersensitivity and significant improvement in gingival and plaque scores was evident after full coverage. Irrespective of the material used, full-coverage crowns are a viable option torestore severely affected hypomineralized teeth. | More prospective trials with a larger sample size and a longer follow-up. |
| Dhareula et al. 2019 India | Cumulative survival rates were high and both materials had very good results showing to be a predictable and conservative restorative alternative treatment for MIH. | Restoration survival: (no difference) | not mentioned | the failures were more cohesive (inside of the enamel) than in the interface. Irrespective of the type of material used, onlays offer a predictable and conservative restorative alternative for molars with MIH. | Long follow-up to define the supremacy of one material over the other |
| de Souza et al. 2017 Brazil | No difference between groups. These protocols can be indicated for conservative cavities. | Restoration survival: (no difference) | In the Self-etch group failures were higher in the upper teeth. Total-etch group showed no difference. | Failures were attributed to marginal adaption, retention, and secondary carious. | Further studies are needed to evaluate the clinical survival of composite resin and Glass ionomer restorations in a sound enamel and hypomineralized enamel |

* Abbreviations used in this table: MIH=molar incisor hypomineralization; PEB=posteruptive enamel breakdown.

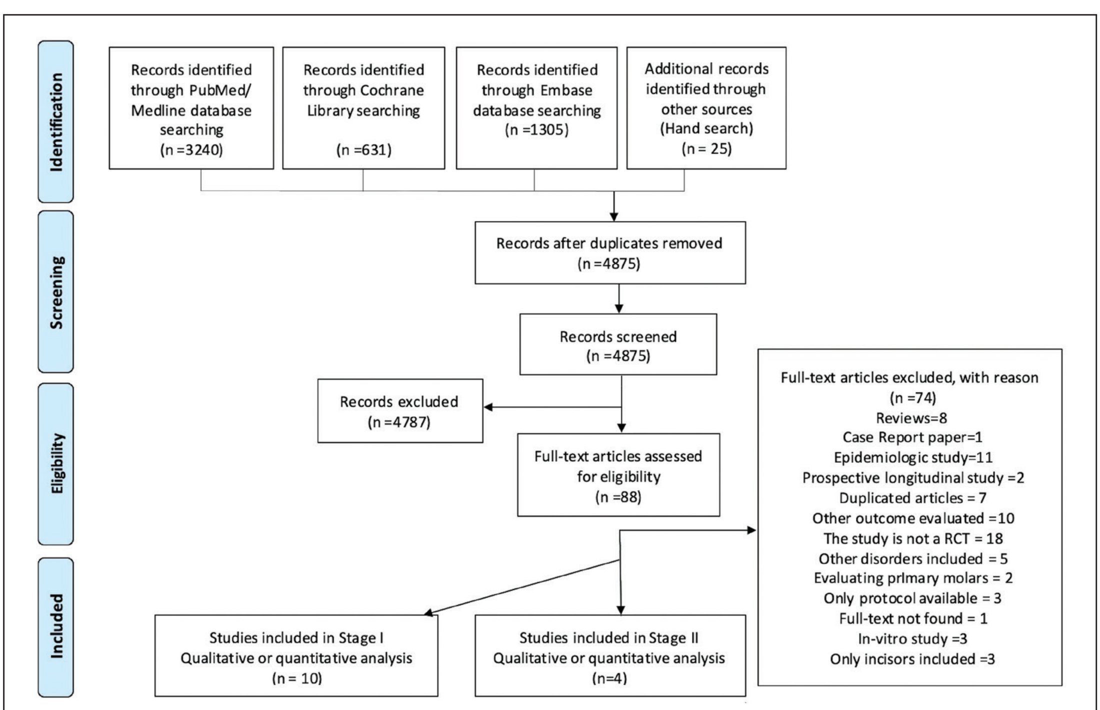


Figure 1. PRISMA flow diagram of the screening and selection process.

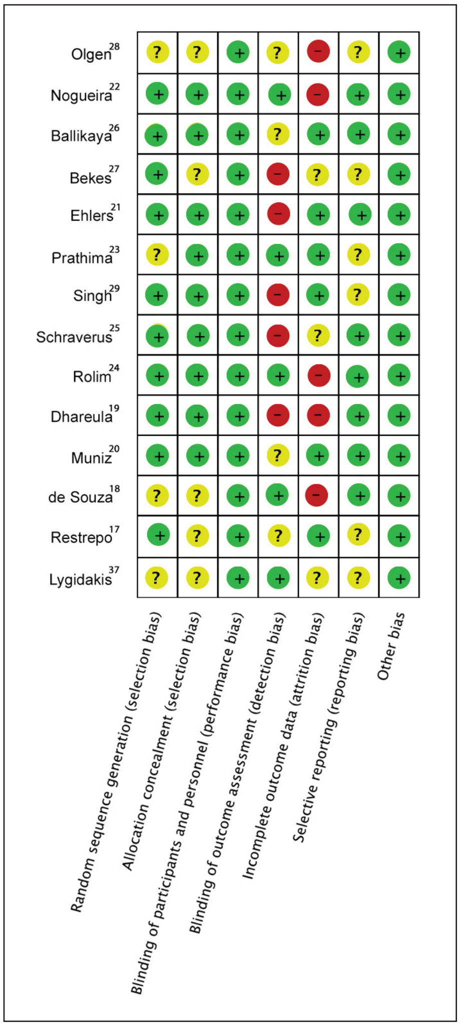


Figure 2. Risk of bias summary: review authors' judgements. The color represents the reviewer's conclusion about the risk of each type of bias in each study: red=high risk of bias; yellow=unclear risk of bias; green=low risk of bias. The figure shows that nine studies were classified as high risk of bias and six studies were classified as unclear risk of bias.

provided better remineralization than the control group after 24 months,[28] agents containing casein phosphopeptide amorphous calcium phosphate (**CPP-ACP**) and casein phosphopeptide amorphous calcium fluoride phosphate (**CPP-ACFP**) were more effective than five percent NaF varnish. Moreover, Restrepo et al.[17] showed no difference between groups comparing NaF varnish with the control group for one month.

Structural integrity maintenance was measured in five studies[17,22,25,26,28] involving 672 MH-affected teeth. Nogueira et al.[22] showed that fluoride therapy did not maintain structural integrity. Schraverus et al.[25] compared glass ionomer (**GI**) sealant with a control group testing for PEB and concluded that GI sealants can prevent dental caries but not PEB.

Three RCTs[20,26,27] evaluated hypersensitivity decrease on resin-based and GI sealants; 290 MH-affected molars and incisors were evaluated. Bekes et al.[27] concluded that GI and resin sealants reduced hypersensitivity successfully in 12 weeks. Ballikaya et al.[26] found lower hypersensitivity scores using silver diamine fluoride (**SDF**) and silver modified atraumatic restorative technique (**SMART**) sealant in two months for both groups. Muniz et al.[20] showed that the combination of laser and fluoride had greater desensitizing action.

Four studies[25-28] measured decay prevention on 506 MH-affected molars. Olgen et al.[28] found no decay in pits and fissures within the fluoride group and control group. Also, no decay was found in the CPP-ACP and CPP-ACFP groups. Comparing SDF with SMART sealant,[26] Ballikaya et al.[26] found similar short-term prevention against dental caries.

Four studies[16,25-27] evaluated retention on 463 MH-affected molars with no PEB. Bekes et al.[27] compared resin-based with GI sealants and showed statistically similar results, but resin was better when comparing marginal integrity and discoloration. Ballikaya et al.[26] concluded that the SMART technique had a reasonable retention rate on occlusal. Schraverus et al.[25] showed a 91 percent success rate in six months and an 83 percent success rate for GI sealant retention. Lygidakis et al.[16] compared the two sealing techniques and showed better retention with the fifth-generation adhesive.

**Severe MH.** Four studies[18,19,24,29] with 207 MH-affected molars evaluated retention. Two studies[18,24] compared self-etch and total-etch direct composite techniques with no statistical difference in survival rate. All materials and techniques studied on severe MH decreased tooth hypersensitivity immediately after treatment was completed. No difference was found between materials, considering the hypersensitivity outcome. Two studies[19,29] utilized indirect restorations to restore MH teeth, obtaining very good results. Dhareula et al.[19] showed a clinical success of 90 percent for cast metal onlay and 85.7 percent for indirect composite onlay in 36 months. The authors reported that failures were more cohesive than on the interface. Singh et al.[29] evaluated full coverage and showed excellent clinical success with 100 percent of retention in all three groups.

## Discussion

This is the first systematic review comparing RCTs that related mild and severe MH to a specific treatment. Determining the severity of the presentation is important to assist clinicians in understanding the different needs of each level and provide the means to better determine the treatment to be followed. Previous systematic reviews on MH were not restricted to RCTs alone, rendering less data homogeneity and a greater risk of bias.

Since the affected teeth are often not completely erupted yet and have wide pulp chambers and high pulp horns, Dhareula et al.[19]and Lygidakis et al.[9] recommend a conservative approach as the first choice. Nevertheless, treatment of MH can be very challenging and clinicians must be able to find the delicate balance between traditional conservative treatment and more invasive options due to the fast course that this condition may present.

On mild MH, treatment aims basically to prolong enamel integrity time with remineralizing agents, prevent breakage and caries, and reduce hypersensitivity. Evidence is still lacking on what the best protocol is and the long-term effect.[17] Even though fluoride is still the gold standard remineralizing agent,[17] CPP-ACP agents seem to demonstrate a faster and better result than fluoride solo on MH.[5,9,28]

CPP-ACP promotes remineralization by delivering calcium and phosphate ions, generating a state of supersaturation of ions. Because casein is a milk protein derivative, CPP-ACP is contraindicated in patients allergic to milk proteins.[9]

Schraverus et al.[25] compared GI sealants with a control group and concluded that they did not prevent enamel breakdown. Nogueira et al.[22] observed that yellow-brown lesions showed a more disorganized prismatic structure with lower mineral density and higher protein content, leading to increased porosity. The authors mostly agreed that the more yellow-brown demarcated opacities a tooth presents, the more prone it is to PEB, regardless of the treatment or material applied.

Table 3. GRADE (GRADING OF RECOMMENDATIONS, ASSESSMENTS, DEVELOPMENT, AND EVALUATIONS) QUALITY OF EVIDENCE

| Number of molars (N)† | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Certainty of the evidence* (GRADE) |
|---|---|---|---|---|---|---|---|
| Outcome 1: Remineralization | | | | | | | |
| 197 (2‡) | Randomized clinical trial | Serious§ | Not serious | Not serious | Serious¦ | Not serious | ⊕⊕OO Low |
| Outcome 2: Structural integrity maintenance | | | | | | | |
| 672 (5‡) | Randomized clinical trial | Serious§ | Not serious | Serious¶ | Not serious | Not serious | ⊕⊕OO Low |
| Outcome 3: Hypersensitivity decrease | | | | | | | |
| 354 (4‡) | Randomized clinical trial | Serious§ | Not serious | Serious# | Serious¦ | Not serious | ⊕OOO Very Low |
| Outcome 4: Decay prevention | | | | | | | |
| 506 (4‡) | Randomized clinical trial | Serious§ | Not serious | SeriousY | Not serious | Not serious | ⊕⊕OO Low |
| Outcome 5: Retention | | | | | | | |
| 670 (8‡) | Randomized clinical trial | Serious§ | Not serious | Very seriousx | Not serious | Not serious | ⊕OOO Very low |

* Certainty of evidence: high ⊕⊕⊕⊕; moderate ⊕⊕⊕O; low ⊕⊕OO; very low ⊕OOO.
† Numbers of molars were used instead of numbers of patients because one patient can have more than one different tooth evaluated.
‡ Numbers of papers addressing this outcome.
§ The certainty of the evidence was downgraded in one level: outcome 1=1 study with unclear risk of bias[17] and another with a high risk of bias[28]; outcome 2=2 studies with unclear risk of bias[17,26] and 3 with a high risk of bias[22,25,28]; outcome 3=2 studies with unclear risk of bias[20,26] and 2 studies with a high risk of bias[24,27]; outcome 4=1 study with unclear risk of bias[26] and 3 studies with a high risk of bias[25,27,28;] outcome 5=2 studies with unclear risk[16,26] and 6 studies with a high risk of bias[18,19,24,25,27,2].
¦ The certainty of the evidence was downgraded in one level because the amount of data was limited. For continuous outcomes, the total number of participants is less than 400.
¶ The certainty of the evidence was downgraded in one level. Two studies[25,26] have interventions that cannot be compared to other studies.
# The certainty of the evidence was downgraded in one level. The interventions compared are different in the three studies. One[27] compared resin sealant and glass ionomer sealant; the other 26 compared silver diamine fluoride and SMART technique restoration; the third20 compared laser, fluoride, and laser and fluoride together; and another compared total-etch and self-etch techniques.[24]
Y The certainty of the evidence was downgraded in one level. Interventions compared are different and only two can be compared in terms of material.[25,27]
x The certainty of the evidence was downgraded in two levels. The interventions are different and incomparable in some cases. One study compared the retention of resin sealants and GI sealants[27]; another study evaluated the retention on ART (atraumatic restorative treatment) restoration using the SMART technique[26]; another study[25] evaluated glass ionomer sealant retention with or without conditioning the enamel; another study[16] evaluated the use of fifth-generation adhesive on sealant technique; two other studies[18,24] evaluated total-etch and self-etch for retention for composite restorations; and 2 studies[19,29] evaluated the retention of indirect restorations. The comparator criteria were not specified in two papers.[16,25]

Furthermore, cusp or incisal involvement also increases the risk of failure related to structural integrity; also, since molars are subjected to greater mechanical forces than incisors, they have higher failure rates. Frequent recall intervals of three to six months and enhanced preventive measures to closely monitor MH teeth have been suggested.[9,22]

Regarding hypersensitivity decrease, almost all materials (CPP-ACP, CPP-ACFP, and fluoride) showed good results.[20,24,26,27] The association of laser and fluoride varnish can be faster and more effective in reducing hypersensitivity.[20] Different materials, such as resin, GI sealants, and SDF, proved to be very effective not only in reducing tooth hypersensitivity but in preventing caries on the occlusal surfaces on mild MH. Marginal discoloration from SDF is a limitation in aesthetic regions.[26]

A specific toothpaste for patients with MH has not been developed yet. However, desensitizing pastes have been used as an adjuvant against hypersensitivity in this type of patient.[21] Ehlers et al.[21] compared the efficacy of hydroxyapatite versus amine fluoride toothpaste in relieving sensitivity. Forty-eight patients with MH-affected teeth were observed for eight weeks and both materials showed very good results, with hydroxyapatite showing fewer symptoms. Bekes et al.[30] compared in a non-RCT the reduction of hypersensitivity after combining a single in-office application and a home-based program with desensitizing products containing eight percent arginine and calcium carbonate. Results on 19 children with affected-MH teeth showed that the proposed protocol was able to relieve the symptoms for eight weeks. Da Cunha Coelho et al.,[3] in a systematic review of hypomineralization treatments including MIH, amelogenesis imperfecta, and dental fluorosis, also agreed with the recommendation for arginine paste as the desensitizing agent to treat hypersensitivity.[3] Larger patient samples and more evidence-based research are still needed regarding effectiveness against sensitivity and agreeable taste for greater compliance, especially in children.

In addition to toothpastes, some companies have launched chewing gums containing agents intended to remineralize tooth structure. Prathima et al.[23] compared the salivary characteristics after chewing gum containing CPP-ACP and gum with xylitol and demonstrated improvement in the salivary properties for both groups. More scientific evidence is needed regarding the use of the gum.

Concerning decay prevention, Olgen et al.[28] observed that five percent Na fluoride varnish, CPP-ACP, and CPP-ACFP demonstrated excellent performance compared to the control group after 24 months, especially in creamy-white defects. The development of caries on creamy-white defects was only seen on fissures, while on yellow-brown defects caries was observed both on fissures and on defect areas. This agrees with other studies.[4,28,31-33]

Adhesion to enamel is a challenge for MH-affected teeth, and most of the studies showed low bond strength values.[34] However, Lygidakis[16] demonstrated that when a fifth-generation prime/bond adhesive agent was added to the conventional etch-and-seal technique for resin sealants, retention was substantially increased in MH-affected teeth. Bekes et al.[27] compared the retention of GI and resin-based sealant. They also used a fifth-generation adhesive for the resin sealants, but did not etch before adhesive application, and achieved very good results in 12 weeks. There seems to be a trend toward fifth-generation adhesive on the resin sealant technique for MH-affected teeth, but the protocol is not yet fully established in the literature and further research is needed.[34]

Four studies evaluated retention of materials on mild MIH with no PEB,[16,25-27] comparing GI and resin sealants. Both materials had a good survival rate in three to 12 months, but composite sealants had better marginal integrity and color stability. Glass ionomer sealants have the advantage of releasing and recharging fluoride, in addition to being a less sensitive technique. The authors[25] stated that sealed molars presented 77 percent less chance of caries than unsealed molars. Some authors also stated that remineralization protocols before applying sealants can increase retention.[18,35]

On severe MH, the aims are to treat decay and sensitivity and restore the teeth. First and foremost, a decision on keeping the affected teeth or not must be made. The best period for extractions is from eight to 10 years old due to the preferable chronological period for spontaneous space closure.[8,9,36] Several factors, such as the number of affected teeth, presence of third molars, the severity of breakdown, and pulpal involvement must be considered. The focus of the present study was to explore the treatments for restorable teeth.

All restorations used on severe MH studies, either direct or indirect, were able to significantly reduce the pain immediately after placement and after 12 to 18 months.[19,24,29] Two studies[18,24] compared the survival of composite restorations when using self-etch or total-etch techniques on severe MH, achieving similar results after 18 months. Both studies used the approach of removing enamel until a probe or bur met resistance.[37] Interestingly, most fractures had cohesive defects in the tooth. Therefore, a conservative approach with direct restorations is still encouraged. If a proximal surface or functional cusp area is not compromised, especially if the tooth presents only white creamy defects, conservative treatment can postpone and even avoid full-coverage restorations.

No RCTs using amalgam were retrieved, but it has been suggested that this material should be avoided on teeth presenting MH. The need for physical retention in these atypically-shaped cavities will probably increase the breakdown of enamel.[3,5,10,38] Elhennawy et al.[10] agreed with that in a recent review, adding that adhesive restorations seem more qualified for this situation but the enamel-adhesive interface is more porous, leading to enamel cracks, decreased bond strength, and a greater number of failures in a shorter period. Also, very limited evidence is available for pulp therapy, specifically in MH-affected molars.

The literature is still scarce regarding the rehabilitation of MH teeth using partial coverage crowns, but it's known that the MH defect rarely affects the cervical part of the tooth structure.[5] Therefore, for extensive losses involving proximal areas and functional cusps, and if molars are not completely erupted, onlays seem to be a better and more conservative alternative.[19]

Although full-coverage restorations are considered the least conservative technique, in cases with extensive structural loss and yellow-brown enamel this can be the best treatment.[29] In 2022, Singh et al.[29] performed an RCT comparing three different materials for full-coverage restorations: zirconia, lithium silicate, and metal cast. They observed 100 percent success in retention after 12 months and 100 percent decay prevention after 24 months. The study also demonstrated significant improvement in gingival and plaque scores after full coverage. Lygidakis[9] pointed out three main categories of indirect restorations for MH teeth with good longevity: metal alloys, indirect composite, and ceramic restorations. The trade-off is that indirect techniques always require longer chair time and increase treatment costs.[9]

No RCT evaluating prefabricated stainless steel crowns has been found. However, three non-RCTs[39-41] have suggested that these crowns can be an alternative approach for severe cases or temporary treatment in extensively destructed teeth that are planned to be extracted but have not yet reached the ideal age for extraction.[9,42]

Therefore, the greatest strengths of the present systematic review are that it analyzed the largest number of RCTs on MH than any other previous review[16-29] and it provides a clear correlation between disease classification, treatment plan, and prognosis.

Some limitations of the present study should be acknowledged. First, the RCT studies retrieved many different interventions, without a linking factor, making a network meta-analysis unfeasible to identify the best approach for the different severities. Second, the analysis of the risk of bias showed that included studies presented an unclear and high risk of bias. Third, the certainty of the evidence was found to be of low quality for the three outcomes and very low quality for the two outcomes. Also, significant variations, such as the extent of defects, methods, and follow-up periods made the comparison difficult. Further RCTs with longer follow-ups, low risk of bias, higher certainty of evidence, and standardized methodology are needed. To reduce the risk of bias, more attention needs to be given to define better sequence generation, allocation concealment, and outcome selection. According to GRADE, the sample size needs to be increased (imprecision), comparator criteria need to be better specified for the outcomes, and more RCTs need to be performed with similar or better comparable interventions (indirectness).

## Conclusions

Based on this study's results, the following conclusions can be made:

1. Successful preventive and treatment options were studied and identified for the different patterns of molar hypomineralization.
2. Mild MH needs remineralization, desensitization, sealants, and close monitoring.
3. Severe MH requires a restoration to treat hypersensitivity, reconstruct the affected teeth, and protect against further deterioration.
4. Yellow-brown defects have the poorest prognosis.

## Acknowledgments

The authors wish to thank Dr. Fabio Ritto, DDS, MD, MS, PhD, Professor and Program Director, Oral Surgery Department, and Dr. Divesh Sardana, BDS, MDS, MBA, PhD, MPH, Clinical Assistant Professor, Pediatric Dentistry Department, both at the Oklahoma University College of Dentistry, Oklahoma City, Okla., USA, for their critical reading of the manuscript and for Dr. Sardana's guidance on GRADE certainty of evidence; and Sheryl Lynn Hamilton, Assistant Professor of Research, Health Sciences Library and Information

Management University of Oklahoma Health Sciences Center, Oklahoma City, for collaborating with all the work related to the bibliographic searches and search strategies of this systematic review.

**Disclaimer.** The authors have no conflicts of interest to declare.

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