




Rehabilitation Treatment in Pediatric Patients with Molar Incisor Hypomineralization: A Scoping Review

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ABSTRACT

Objective: To identify the available evidence on the different treatment types for the rehabilitation of MIH-affected teeth in children. **Material and Methods:** A search was carried out in Pubmed, Cochrane Library, Epistemonikos, Lilacs and Google Scholar. Observational studies published until June 2022 were included. Two reviewers independently screened studies and extracted data. **Results:** 1593 studies were screened and a total of 38 articles were included, which were mainly case reports published in Brazil. Most included studies concluded that the evaluated treatment was "beneficial" or "probably beneficial". Reported treatments included: glass ionomer cements (GIC), composite resin restorations, preformed metal crowns, laboratory fabricated crowns, microabrasion management of incisors and resin infiltration. **Conclusion:** Successful treatment options have been identified, such as GIC as a provisional restoration for severe cases and for uncooperative children; restorations with composite, indirect restorations, or preformed metal crowns also seem suitable treatment options for young patients diagnosed with MIH. There is still little evidence to support an approach for anterior teeth affected by MIH.

Keywords: Molar Hypomineralization; Dental Enamel Hypoplasia; Therapeutics; Molar.

Introduction

Molar incisor hypomineralization (MIH) is characterized by the presence of qualitative defects, such as discrete demarcated enamel lesions, affecting at least one permanent first molar with or without incisor involvement [1,2]. Various systemic, genetic and /or environmental factors have been associated with MIH, revealing a multifactorial etiological model [3]. Perinatal (hypoxia, caesarean section, and prematurity) and postnatal (measles, urinary tract infection, bronchitis, otitis media, gastric disorders, kidney diseases, pneumonia, and asthma) etiologic factors are considered to be more likely to increase the odds of MIH development compared to prenatal factors [3]. Clinically, hypomineralization is characterized by opacities of variable size that can change color from white to yellow/brown [4].

Teeth affected by MIH present wide variations according to their severity [5]. The mild form is associated with delimited opaque areas, varying from white to brown, especially in molars; this form generally does not present structural loss or major dental sensitivity [6]. The moderate form presents mild or null dental sensitivity, and the severe form mainly occurs at the level of the third occlusal/incisal, leading to post-eruptive degradation due to hardness reduction and high enamel porosity [6].

MIH affected teeth are often extremely sensitive to thermal and mechanical stimuli influencing children's quality of life by increasing their risk to develop caries, their susceptibility to breaking their teeth, failure of bonding to materials, as well as influencing on their behavior [5,7,8]. In addition, treatment may be more painful due to difficulties in applying local analgesia (due to altered nerve potential) and chronic subclinical inflammation caused by enamel porosity [5].

The management of MIH is a challenge for pediatric dentists due to its clinical appearance and treatment needs, thus knowing more on different treatment options (e.g., composite resin restorations, glass ionomer cements, metal crowns, indirect laboratory-manufactured restorations, etch-bleach-seal technique, etc.) [9], and their effectiveness may help to improve clinical outcomes on these patients. Especially, considering factors such as the cooperation of the patient, the stage of dental development, the severity of the defect, and parental preferences, among others [10].

The objective of this review is to identify the available evidence on the different treatment types for the rehabilitation of teeth affected with MIH in pediatric patients.

Material and Methods

This review was conducted according to the Joanna Briggs Institute's Reviewers Manual for JBI Scoping Reviews [11]. The protocol of this study is registered at OSF (<https://osf.io/6yjbn/>).

Eligibility Criteria

The inclusion criteria for this scoping review were observational studies (cohort, cross-sectional, clinical case, case series), systematic reviews, and randomized clinical trials; studies focused on caries treatment in hypomineralized molars or incisors in children between 6 and 16 years of age; articles published in English, Spanish and Portuguese. Studies on temporary teeth and other types of tooth enamel defects were excluded.

Search Strategy

A systematic search was performed in the following electronic databases: Pubmed, Cochrane Library, Epistemonikos and Lilacs using keywords and controlled terminology (MESH). We also searched in Google Scholar as part of the grey literature. We searched for articles published up to January 2022.

Study Selection

Two reviewers (DMT, OJC) independently selected research articles by title and abstract after duplicates were removed. Disagreements were solved by discussion between the two reviewers or by consulting a third reviewer when needed (CMG). The full-text version of relevant articles was retrieved and independently selected by the two reviewers according to the inclusion criteria. The selection process was carried out using the Rayyan online software.

Table 1. Full search strategy.

Databases	Keywords
PubMed/Medline	((((child*[MeSH Terms]) OR (child*[Title/Abstract])) OR (pediatric patient [MeSH Terms]) OR (pediatric patient [Title/Abstract])) AND (((hypomineralization, molar incisor[MeSH Terms]) OR (molar incisor hypomineralization[MeSH Terms]) OR (molar incisor hypomineralization[Title/Abstract])) OR (mih[Title/Abstract])) AND ((treatment[MeSH Terms]) OR (treatment[Title/Abstract]))
Epistemonikos	title:(title:(title:(title:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization))) OR abstract:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization)))) OR abstract:(title:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization))) OR abstract:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization)))) OR (title:(title:(mih) OR abstract:(mih)) OR abstract:(title:(mih) OR abstract:(mih)))) OR abstract:(title:(title:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization))) OR abstract:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization)))) OR abstract:(title:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization))) OR abstract:(title:(molar incisor hypomineralization) OR abstract:(molar incisor hypomineralization)))) OR (title:(title:(mih) OR abstract:(mih)) OR abstract:(title:(mih) OR abstract:(mih)))) AND (title:(title:(title:(child*) OR abstract:(child*)) OR abstract:(title:(child*) OR abstract:(child*))) OR (title:(title:(pediatric patient) OR abstract:(pediatric patient))) OR abstract:(title:(pediatric patient) OR abstract:(pediatric patient)))) OR abstract:(title:(title:(child*) OR abstract:(child*)) OR abstract:(title:(child*) OR abstract:(child*))) OR (title:(title:(pediatric patient) OR abstract:(pediatric patient)))
Cochrane	((Child[Mesh] OR (child*) OR (pediatric patient)) AND ((Molar incisor hypomineralization) OR (mih)) AND((Therapeutics[Mesh] OR (Treatment
Lilacs	tw:(tw:(hipomineralización de los dientes)) AND (tw:(hipoplasia del esmalte dentario)) AND (tw:(niños))
Google Scholar	"Molar incisor hypomineralization" AND "children" AND "treatment" AND "restorative"

Data Extraction

Two reviewers (DMT, OJC) independently extracted data on an Excel spreadsheet, including: author, year of publication, country of origin of the study, study design, objective of the article, MIH concept, sample size, sample age, main results and conclusions.

Results

We screened 1593 studies from the systematic search after duplicates were removed. One thousand sixty-five articles were excluded by title and abstract and 144 articles were screened by full-text. In total, 38 articles were included in this scoping review (Figure 1).

The main characteristics of the included studies are displayed in Table 2. These studies were published between 2010 and 2022, and most of them come from Europe [10,12-27] and Brazil [5,28-38]. In terms of the included studies' design, 20 were case reports [8,13,15,16,19,25-27,31,33-35,38-44], 7 were cohort studies [14,18,20,21,23,28,36]; 7 were randomized controlled trials [5,17,24,29,32,45,46] and 4 were systematic reviews [10,12,22,37]. The age range of the included sample was between 6 and 16 years old.

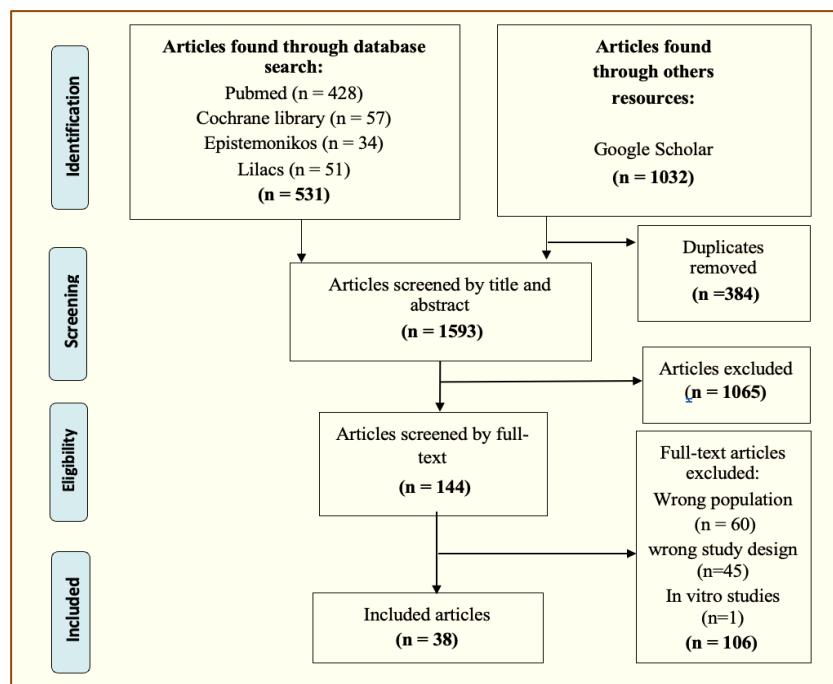


Figure 1. PRISMA flowchart describing the study selection process.

Most authors of the 38 included studies define MIH as a qualitative defect of the dental enamel, which causes disintegration of the occlusal surfaces and cusps [13,14,16,18,19,22,24,26,28,31-34,36,45]. Several studies also mentioned that MIH is characterized by creamy white, yellow or brown opacities affecting one or the first four permanent molars frequently associated with the permanent incisors. In addition, this condition is mainly considered to be of systemic etiology, attributed to the interrupted ameloblastic activity that occurs during the pre-eruptive maturational stages of amelogenesis [31,46]. However, a study carried out by Harika et al. [40] added that enamel defects in MIH may be also caused by local, genetic or environmental factors or even due to multiple factors, while other studies agreed that MIH is the result of the synergistic action of environmental factors and genetic expression, especially, genetic polymorphisms that begin prenatally and persists throughout childhood [5,40].

In addition, we mapped the scope of evidence using a bubble plot (Figure 2). Each bubble on the chart represents an included study. The graph shows information about the authors' conclusions in the X axis ("unclear", "no effect", "probably harmful", "harmful", "probably beneficial" and "beneficial") (Table 3), while the Y axis represents the study type, and the bubble size represents the number of teeth involved in the studies.

Out of the 38 included studies, 12 studies assessed glass ionomer cement and eight concluded that this material is "beneficial" [8,13,28,29,31,33,41,42], three studies concluded that it is "probably beneficial" [14,23,30], and one study concluded that its effects are "unclear" [26]. In terms of composite resin restorations, nine studies concluded that it is "beneficial" [18,19,21,24,27,34,38,40,44], one described it as "probably beneficial" [35], and two concluded that this material had "no effect" [5,32]. Additionally, four studies evaluating indirect restorations and full coverage crowns concluded that this treatment is "beneficial" [16,39,45,46]; four studies assessing stainless steel crowns also concluded that this treatment is "beneficial" [15,17,36,43]; while two studies that evaluated microabrasion, whitening and infiltration of resin concluded as that these are "probably beneficial" [20,25]. Three systematic reviews evaluated the different restorative materials in MIH, concluding these treatments as "probably beneficial" [10,12] and "unclear" [37]; one SR study evaluated the bond strength of the composite to the MIH affected enamel and concluded as "no effect" [22].

Table 2. Characteristics (author, type of study, country, age range and objectives) of included studies.

Author	Study Design			Country	Sample Age	Rehabilitation Treatment for MIH	Etiology			Type of Teeth Affected		
	RCT	Cohort	Case Report SR				Systemic	Multifactorial	Unknown	Incisor	molars	Incisor/ molars
Arce_Izaguirre et al. [41]			X	Peru	7 years	To evaluate the use of fluid giomers in a posterior tooth with loss of structure diagnosed with MIH.		X				X
Assunção et al.[35]			X	Brazil	7 years	To evaluate the longevity of restorative treatment through the use of composite resin in incisors and molars with MIH.			X			X
Bagattoni et al. [13]			X	Italy	6 years	To evaluate a conservative and provisional treatment through the use of an orthodontic band with cementation of glass ionomer cement.	X					X
Davidovich et al. [39]			X	Israel	8 years	To evaluate the treatment for children with MIH using a digital workflow with IOS (intraoral scanner) and CAD-CAM (computer-aided design and computer-aided manufacturing).		X				X
Dhareula et al. [46]	X	—		India	8-13 years	To compare the performance of minimally invasive cast metal and indirect resin inlays for the rehabilitation of first permanent molars with severe MIH.		X	—			X
De Oliveira et al. [30]			X	Brazil	7 years	To clinically evaluate glass ionomer cement restorations within 6 years which were then replaced by composite resin due to wear and recurrent caries.	X					X
Durmus et al. [14]	X			Turkey	8 years	To evaluate the survival and clinical performance of high-viscosity glass ionomer after selective removal of carious tissue in molar incisor hypomineralization.	X					X
De Farias et al. [36]	X			Brazil	7-10 years	To evaluate the survival of restorations with stainless-steel crown or composite resin in first permanent molars affected by MIH for 24 months		X	—			X
De Hoyos et al. [44]			X	Mexico	8 years	To evaluate the adhesive alternatives and their wide usefulness in this enamel defect as well as the correct use of adhesive agents.			—			
Fragelli [28]	X			Brazil	6-9 years	To evaluate the clinical performance of glass ionomer restorations in teeth with MIH.	X					X
Fernandez et al. [15]			X	Spain	9 years	To evaluate the effectiveness of the use of glass ionomer cement and the placement of metallic coronas in cases of severe MIH.			X		X	
Feierabend et al. [16]			X	Germany	6-15 years	To evaluate una rehabilitation in combination with no or minimally invasive preparation and pleasing esthetics in severely compromised teeth.		X				X
Futterer et al. [17]	X			Germany	8.5 years	To demonstrate the effects of different therapeutic strategies for teeth with MIH.		X				X
Gatón-Hernandez et al. [18]	X			Spain	6-8 years	To evaluate treatment efficacy using a minimally invasive approach in permanent molars with MIH.	X					X
Grossi, Cabral [29]	X			Brazil	7-13 years	To evaluate restorations' survival rate with hybrid glass restorative system using the atraumatic restorative treatment (ART) in first permanent molars with MIH.	X					X
Hahn et al. [19]			X	Germany	11 years	To evaluate the management of molar incisor hypomineralization from the mixed to the permanent dentition stage.		X				X
Hasmun et al. [20]	X			UK	7-16 years	To evaluate the quality of life through minimally invasive aesthetic treatment for masking the visibility of incisor opacities in children with MIH.	X					X
Harika et al. [40]			X	India	13 years	To evaluate the functional and aesthetic rehabilitation of a 13-year-old girl diagnosed with multiple developmental defects of enamel.		X				X

Kotsanos et al. [21]	X	Greece	7 years	To assess the treatment management of first permanent molars in children with MIH.	X	X
Lagarde et al. [22]	X	France	6-12 years	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 optimize the bonding to this hypomineralized enamel and to determine which is (are) the best bonding protocol.	X	X
Linner et al. [23]	X	Germany	11 years	To evaluate survival rates using conventional non-invasive (GIC) and definitive treatment strategies (composite, CAD / CAM ceramic restorations).	X	X
Lygidakis et al. [24]	X	Greece	8-10 years	To evaluate the clinical performance of complex composite restoration placed on permanent molars with MIH.	X	X
Lygidakis [12]	X	Greece	6-16 years	To review the literature concerning the treatment of MIH, shortcomings and areas of future research.	X	X
Lopes-Fatturi [37]	X	Brazil	7-10 years	Evaluate the success of the restored treatment performed with different materials in molars with HIM.	X	X
Mejia-Herrera et al. [43]	X	Peru	8 years	To evaluate the possible rehabilitation options in cases of MIH through the use of preformed steel crowns and composite resin restorations	X	X
Mendonça et al. [33]	X	Brazil	11 years	To evaluate the adapted technique of simplified occlusal replication with conventional glass ionomer cement posterior teeth in a child with severe MIH.	X	X
Orellana et al. [8]	X	Chile	11 years	To evaluate the retention and resistance of the resin-modified glass ionomer and orthodontic band to occlusal forces with an 18-month follow-up in cases of severe MIH.	X	X
Prud'homme et al. [25]	X	France	7-12 years	To evaluate the effectiveness of the etch-bleach-seal technique for the treatment of MIH opacities at the incisor level.	X	X
Pérez-Vasquez, Allende-Trejo [26]	X	Spain	9 years	To evaluate the effectiveness of using type 2 glass ionomer and ionomer-based fissure sealants in severe MIH.	X	X
Restrepo et al. [34]	X	Brazil	12 years	To evaluate a conservative and minimally invasive technique for the aesthetic management of MIH in anterior teeth with different degrees of severity, achieving favorable aesthetic results after one year of monitoring.	X	X
Romo [42]	X	Ecuador	8 years	To evaluate the pieces with MIH the same ones that were restored with glass ionomer cement and consider in a future possible restoration with inlays or coronas from 16 years of age.	X	X
Rolim et al. [32]	X	Brazil	7-16 years	To evaluate the survival of direct restorations on first permanent molars with MIH and the impact of treatment on self-reported dental pain.	X	X
Sabrosa et al. [38]	X	Brazil	11 years	To assess the clinical survival of the restoration of a permanent first molar with MIH using a preformed malleable composite resin crown.	X	X
Singh et al. [45]	X	India	8-15 years	To evaluate and compare the clinical performance of full coverage crowns on first permanent molars affected with MIH.	X	X
de Souza et al. [5]	X	Brazil	6-8 years	To evaluate the clinical survival of direct composite resin restorations in teeth with MIH compared with two adhesive systems (self-etching and total etching).	X	X
Somani et al. [10]	X	UK	6-10 years	Systematically evaluate the success of treatment modalities for molars and incisors affected by MIH.	X	X
Takahashi et al. [31]	X	Brazil	7 years	To evaluate restorations with different types of glass ionomer in teeth with MIH.	X	X
Temudo et al. [27]	X	Portugal	9 years	To evaluate restorations in situations such as hypersensitivity and esthetics in MIH.	X	X

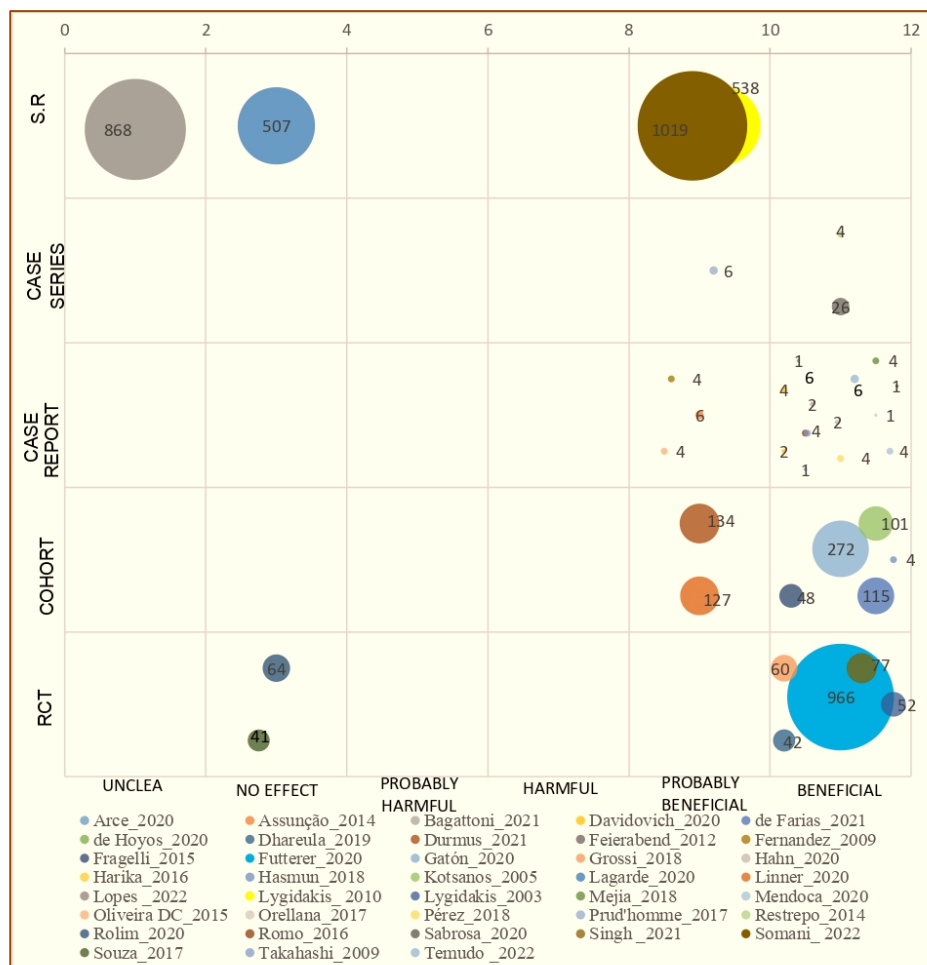


Figure 2. Bubble plot of the included evidence showing the study design, its sample size and the study’s conclusion.

Table 3. Classification of studies’ conclusions.

Beneficial	The study conclusions claim a beneficial effect without major adverse effects and without major concerns regarding the supporting evidence.
Probably Beneficial	The study conclusions do not report strong benefits despite the positive effect of the treatment.
Harmful	The study conclusions clearly indicate a harmful effect.
Probably Harmful	The study conclusions do not report a strong harmful effect despite the negative effect of the treatment.
No Effect	The study conclusions report that there is no difference between intervention and comparator.
Unclear	The study conclusions do not report one direction of the results due to conflicting results and limitations among individual studies.

In total, seven studies were RCT with a total of 1302 MIH teeth; there were seven Cohort studies that included 811 dental pieces; there were 20 case reports with 90 MIH teeth, and finally, four were two RS with a total of 2 932 MIH teeth.

Discussion

This scoping review included 38 studies published up to June 2022, which assessed different treatment options to restore MIH-affected teeth. According to the European Academy of Pediatric Dentistry (EAPD) and to experts who frequently deal with children presenting MIH, treatment decisions depend on the severity of the condition, dental age of the patient, expectations of both parents and children and the social origin of the

parent/child [47]. It has been recently highlighted that the defects' severity and the patient's age [9] are two main factors to be considered when treating children with MIH. In general, MIH causes aesthetics and hypersensitivity problems due to enamel rupture after teeth eruption, favoring the progression of caries leading to pulp involvement [4,48-50].

Based on the results obtained from the included studies, glass ionomer cement (GIC) can be used when moisture control is difficult, when the patient lacks cooperation, and in the early stages of the eruption, but its use should be limited in areas that support stress [9,47]. The use of GIC is helpful to increase patients' cooperation until they are mature enough for subsequent invasive and long-lasting treatments [23]. Fragelli et al. [28] showed that the probability to maintain the integrity of the dental structure in molars affected by MIH and restored with GIC is high, reporting a success rate of 78% at 12 months using a non-invasive approach. On the contrary, Linner et al. [23] showed lower survival rates of only 7% [23]. However, restorations' success and longevity could be influenced by the type of GIC, such as hybrid glass restorations, which result in a 98.3% success rate after 12 months of follow-up [29], or through the use of high-viscosity GIC, which has a success rate of 87.5% [14]. Additionally, Orellana et al. [8] suggested the use of resin-modified glass ionomer, which does not cause any symptom for at least 18 months, while Arce-Izaguirre et al. [41] recommends the use of fluid ionomers, a new technology that combines previously reacted GIC and composite resin to obtain both of their properties, resulting in a more economical and resistant material compared to conventional ionomers.

In terms of composite resin restorations, several authors [18,19,21,24,27,34,35,40] use composite resin restorations as a predictable option, with high success rates, if placed under a rubber dam to ensure good moisture control [9]. This minimally invasive approach has been proposed for severe cases of MIH followed by cavity filling with GIC for six months and then restoration with composite resin, achieving a high clinical and radiographic success rate of 96.8% at 24 months [18]. However, Lygidakis et al. suggest a total removal of the hypomineralized enamel for a successful restoration, especially to achieve an optimal sealing, considering that the remaining enamel adhesion affected by MIH is poorer due to a reduced bond strength [9,19,21,24,44]. In addition, composite restorations seem to be the most suitable material since they adhere to the enamel without the need for retentive preparations [51]. When using total etching (with 37% phosphoric acid) and self-etch (without prior etching), no significant differences in survival rates of resin restorations have been found [5,32].

Laboratory-fabricated full-coverage restorations (zirconium crowns, lithium disilicate, and CAD-CAM-fabricated restorations) have recently been used to restore severely affected teeth by removing all decayed and hypomineralized enamel with clinical, long-lasting success after treatment with 24 months long evaluation; longer follow-up is required to reach a definitive conclusion [39,45]. However, available evidence suggests that laboratory-made restorations could be considered a more effective and long-term option, especially in older children when multiple surfaces or cusps are involved [9,10]; but drawbacks such as the extraction of more dental tissue, the difficulty of repair and higher costs must be considered when making the decision on using this technique [10]. Additionally, stainless steel crowns have been shown to be an alternative approach for severely affected molars, with a higher 24-month survival rate, but with other implications such as an increased overbite [10,15,16 36].

Treatment options for incisors affected by MIH have also been discussed in the included papers. According to Lygidakis et al. [9], a minimally invasive approach is important in children due to the large pulp chambers, high pulp horns and immature gums, including the preservation of tooth structure for future restorations [9]. The use of bleaching (10% carbamide peroxide) and remineralization to decrease enamel

opacities can increase the retention and durability of composite restorations bonded to hypomineralized enamel; however, more long-term studies are needed to find out whether there can be negative implications for this treatment type [40]. The etch-bleach-seal technique is a minimally invasive approach that can be used to remove yellowish-brown stains at the incisor level with MIH [9]. However, aesthetic gain is not guaranteed due to the deeper location of the defect [25].

Overall, included studies were mainly case report studies, which concluded that the evaluated treatment was "beneficial" or "probably beneficial", such as the case of glass ionomer cement, or composite resin restorations (as long as there is a complete removal of hypomineralized tissue to increase the longevity of the restorations). Indirect restorations manufactured in the laboratory were mainly classified as "beneficial" as they can be used when there are multiple affected surfaces and they have been associated with high survival rates. In addition, preformed metal crowns have been described as an alternative method for severely affected molars since they can maintain teeth's structural integrity. However, this result is only supported by four studies included in this review, which additionally describe a decrease in sensitivity as a side-effect [15,17,36,43].

The main strength of our scoping review is that we performed an exhaustive systematic search on several databases to bring all available evidence on clinical studies about the different treatment options that exist for children with MIH. Thus, we provided a full overview of studies on this subject that have been developed over the last two decades, including a diverse young population from different countries, continents and age ranges. However, a limitation we came across in this scoping review is that most included studies have a short follow-up period and small samples, which bring no clear conclusions on the benefit of the different treatment options. Another limitation of this study is that we only included studies published in English, Spanish and Portuguese, which might lead to a reporting bias since other studies on this subject could have been potentially published in other languages which have not been included.




Future studies should aim to develop more randomized clinical trials on the different treatment options and the use of different materials for the management of teeth affected by MIH. To provide reliable conclusions, studies should include a larger sample size and consider a longer-term follow-up regarding the changes in materials' adhesion properties, restoration failures, and quality of life improvement.

Additionally, using the keywords described in the methods section, we identified seven ongoing randomized clinical trials (RCTs) on this topic on the World Health Organization's International Clinical Trials Registry Platform and on clinicaltrials.gov [52-56]. Furthermore, we identified five ongoing systematic reviews in the National Institute for Health Research's International Prospective Register of Systematic Reviews (PROSPERO) [57-60] about the treatment of patients affected by MIH. These results could provide, in the near future, relevant evidence about the clinical question raised in this study.

Conclusion

There are different options for the rehabilitation of teeth affected by MIH; however, most evidence comes from case report studies and few clinical trials despite the high demand for research. Successful treatment options have been identified, such as the use of glass ionomer as a provisional restoration for severe cases and for uncooperative children; restorations with composite, indirect restorations, or preformed metal crowns seem suitable treatment options for young patients who have been diagnosed with MIH. There is little evidence to support any approach for anterior teeth previously affected by MIH.

Authors' Contributions

DMTY 	https://orcid.org/0000-0002-7572-413X	Conceptualization, Methodology, Formal Analysis, Data Curation, Writing - Original Draft and Writing - Review and Editing.
OJC 	https://orcid.org/0000-0001-9632-7320	Data Curation.
CMG 	https://orcid.org/0000-0001-6763-3644	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft and Writing - Review and Editing.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

Financial Support

None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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