Journal of Pharmaceutical Research International

33(50A): 113-125, 2021; Article no.JPRI.75299
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Molar Incisor Hypomineralization from Inception to Intervention–Evidence Based Review

Rana A. Alamoudi [a*]

[a] *Department of Pediatric Dentistry, Faculty of Dentistry, King Abdulaziz University, P.O.Box: 7270, Jeddah 21462, Saudi Arabia.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i50A33387
Editor(s):
(1) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.
Reviewers:
(1) Serghei Covanțev, State University of Medicine and Pharmacy, Moldova.
(2) Dharmashree Satyarup, Siksha 'O' Anusandhan University, India.
(3) Dennis Flanagan, Lugano University of Switzerland, Switzerland.
Complete Peer review History: https://www.sdiarticle4.com/review-history/75299

Review Article

Received 10 August 2021
Accepted 15 October 2021
Published 15 November 2021

ABSTRACT

Background: Molar Incisor Hypomineralization (MIH) is considered a highly prevalent clinical problem worldwide. The etiology of MIH involves a complex interaction between systemic and environmental insults with possible genetic contribution. Early diagnosis is facilitated by collaboration between clinicians responsible for oral health management of the patient and is the key for enhancing the long-term prognosis and quality of life of affected children. MIH management is a formidable oral health challenge due to the wide spectrum of clinical presentation with the need for tailored treatment for the child affected by MIH condition.
Objective: To provide dental practitioners with an updated and evidence-based overview of MIH etiology, diagnosis, and treatments modalities available for its management.
Conclusion: In this review, recent clinical evidence on MIH etiology, diagnosis and treatment is presented. Given recent availability of sophisticated technologies there is an increasing number of treatment modalities now at the fingertips of all oral health clinicians alike, ranging from preventive measures, management of hypersensitivity to advanced restorative techniques. The tailored treatment plan should encompass a short and long-term approach requiring more frequent dental check-ups in order to achieve better outcomes and prognosis. Future translational clinical research to best practice that will enhance our understanding of the exact causes of MIH and allow development of standardized diagnostic criteria as well as optimal treatment strategies are warranted.

**Corresponding author: E-mail: rasalamoudi@kau.edu.sa;*

Keywords: Hypomineralized tooth; hypersensitivity; molar incisor hypomineralization; MIH prevalence; MIH diagnosis; MIH treatment.

1. INTRODUCTION

Enamel development (amelogenesis) is a tightly regulated biological process that occurs through mineral deposition in form of hydroxyapatite crystals by the epithelially-derived cells called ameloblasts. Environmental insults, systemic exposures or inherited conditions are known to perturb amelogenesis. [1] Hypomineralization is one of the most common dental defects of developmental origin resulting from disturbances in ameloblast activity during various stages of enamel formation. [2] Molar incisor hypomineralization (MIH) in particular is among the foremost misdiagnosed dental conditions among children that have taken the spotlight in recent years and needs to be addressed in pediatric dentistry.

Originally reported nearly two decades ago, the term MIH described distinct enamel with varied severity of discolored demarcated opacities of systemic origin affecting at least one permanent molar and commonly present with affected incisors. [3] Based on this definition, in 2003 the European Academy of Pediatric Dentistry (EAPD) developed a set of guidelines for diagnostic classification of MIH according to exhibited enamel characteristics. [4] Hubbard and colleagues further coined MIH as an emerging socio-economic burden and a 'silent public health' concern. These enamel defects tend to fracture during eruption and cause not only dentin hypersensitivity but also increased susceptibility to caries. [5] Therefore, given the burden of disease and high prevalence of MIH in some populations, [6-7] the cost of these conditions to the affected families as well as the general community can be substantial.

The EAPD definition and set of diagnostic guidelines for MIH are considered to be limited in that they do not take into account the extend of enamel defects. [8] In addition, while MIH diagnosis is reported by some studies based on the presence of at least one affected first permanent molar (FPM), other studies have based the diagnosis on affected anterior teeth when an affected FPM was not present. [6] The presence of hypomineralization in other teeth including the second primary molars, cusp tips of second permanent molar and canines have been reported. [5] Furthermore, evidence from several studies and systematic reviews indicate hypomineralized second primary molars are highly predictive of MIH with a 33% increase in incidence of MIH if an affected primary tooth is diagnosed. [9-11] Consequently, a number of studies have adopted other terminologies and suggest that incisor hypomineralization (IH), molar hypomineralization (MH) or deciduous molar incisor hypomineralization (DMH) terms which take into account all the other affected teeth should be included as part of the MIH spectrum. [6, 12] In addition, there is inconsistency in applying diagnostic criteria that quantifies MIH enamel defects. While some studies report using EAPD system, others have applied modified criteria to include severity level of MIH or developed their own diagnostic criteria to account for extent of the defect. [6, 13] Despite these discrepancies, the prevalence of MIH remains high in the pediatric population and requires early diagnosis with the identification of 'at risk' MIH populations crucial for optimal management of the condition in these children.

The aim of this review is to provide dental practitioners with an updated and evidence-based overview of MIH etiology, diagnosis, and treatments modalities available for its management.

1.1 Evidence for Prevalence and Etiological Factors

Historically, MIH has been identified dating back to the medieval times [14] with the first epidemiology study of children reported by Koch nearly forty years ago. [15] As a global concern, MIH has highly variable rate of prevalence up to 40% according to different studies. This is likely due to differences in methodology, diagnostic criteria, age groups of the study population and regional factors [16] making it challenging to determine the prevalence accurately. [17] The prevalence of MIH ranges from approximately 2% to 8% in Bulgaria, [18] Germany, [19] Hong Kong, China, [20] Poland [21] and Saudi Arabia, [22] 12% to 19% in Canada, [23] Kenya, [24] Norway, [25] Finland [26] and Indonesia, [27] and 27 to 40% in Dubai-UAE, [28] Tanzania, [29] Denmark [30] and Brazil [31] in ascending order respectively.

Despite, the exact etiological factors for MIH not completely elucidated, during infancy period an association of MIH with childhood illnesses in

particular ear-nose-throat disorders, and antibiotics has been reported. [32] Furthermore, children affected with MIH have been found to be ill more frequently during early childhood; [33-34] episodic otitis media present with high fever specially during the first few years of childhood has been associated with disruption of ameloblast activities during mineralization of the enamel. [35] Moreover, as a result of nutritional deficiencies that occurs during bouts of diarrhea or high fevers, depletion of important minerals such as calcium phosphate has been found to be associated with MIH. [36] Other studies have reported insufficient oxygen supply during birth, combined with common conditions in childhood such as asthma, cystic fibrosis, as well as caesarean delivery or preterm birth in conjunction with environmental insults are significant risk factors and associated with predisposition to MIH. [15, 33, 37-39].

In addition to individual studies, several systematic reviews and meta-analysis have found accumulating evidence to support an association of MIH with early childhood illness and in particular fever, [39-41] as well as hypoxia, hypocalcemia and amoxicillin. [41] However, MIH correlation with peri and prenatal factors is less clear. An earlier systematic review found only limited evidence for an association with the perinatal factors (e.g. birth complication) and prenatal factors (e.g. maternal medication use and smoking). [40] Similarly, an independent systematic review did not find any evidence for MIH associated with maternal systemic exposure to medications. [42] However, apart from fever and early childhood respiratory diseases, a more recent meta-analysis reported significant association of MIH with perinatal factors such as maternal illness, stress, and birth related complications. [39] Furthermore, another systematic review and meta-analysis found evidence for a significant correlation between MIH prevalence and low birth weight and premature birth. [43] Of note the meta-analysis only included four studies due to the significant heterogeneity among other the eligible studies. Since pooling of studies in a meta-analysis provides a higher level of evidence with statistical significance compared to systematic reviews, these findings linking MIH to maternal related as well as perinatal factors need to be explored further. Clinical implication of identifying MIH etiological origins not only contributes to our understanding of the condition but more importantly will guide us in implementing preventive measures for children at potential risk. Table 1 summarizes available evidence reported in recent systematic reviews and meta-analyses on prevalence, etiology, and diagnosis of children with MIH condition.

Given that hypomineralization is a common clinical presentation of genetic anomalies of developmental origin such as dentinogenesis imperfecta, and that amelogenesis is tightly controlled by various genes, therefore MIH as a genetic condition seems more plausible than an idiopathic condition. [41, 44-45] The support for a genetic disposition further comes from a recent genome-wide association study that identified a potential genetic locus on chromosome 22 for MIH (SCUBE1 gene). [46] Moreover, MIH features are akin to some form of localized amelogenesis imperfecta with variations in genes expressed during amelogenesis such as ameloblastin (AMBN), amelogenin (AMELX) reported to be involved in enamel hypoplasia [47] and tuftelin (TUFT1) involved in enamel microhardness [48] may have a role in predisposing to or development of MIH experience in children.

The mineralization of the first permanent molars usually commences around birth and completed by the age of 5 years. During this period, the onset of hypomineralization can occur during disruption of enamel maturation stage. [49] Another important putative cause of MIH is presence of oral clefts which are 12 times more susceptible to tooth agenesis external to the cleft area (mandibular posterior teeth) resulting in significant disruption in enamel maturation process. [50] Nevertheless, irrespective of the specific cause of the amelogenesis disruption, during history taking it is important to note any relevant perinatal history or existing systemic conditions and closely monitor children with persistent illness during early years of childhood. [33]

2. DIAGNOSIS

A common feature of MIH is that the hypomineralized enamel tends to be more porous with lack of distinct crystal edges and greater interprismatic space compared to the completed mineralized enamel. [51] The porous hypomineralized enamel may also result in dentinal hypersensitivity [32] and enamel breakdown post-eruption due to masticatory forces. [52] Apart from functional impairment, patients experiencing MIH often have compromised quality of life as a direct result of

poor esthetics when anterior teeth are involved and recurrent loss of restoration requiring more often dental visits. [32, 53].

As mentioned before, there is currently no standardization of the diagnostic criteria for MIH which takes into account the significant differences in severity of the condition intra and inter individuals. As a result, many studies have reported use of modified criteria to include measure enamel defect or developed a specific scoring system. [5, 24, 54] The current approach to classification of MIH is either according to EAPD scoring system or the Modified Developmental Defect of Enamel (DDE) index which accounts for both type and extent of the enamel defect and divided into 3 distinct categories: demarcated opacities, diffuse opacities, or hypoplasia. [55] A more recent diagnostic approach developed by Cabral and colleagues is based on severity of the MIH (MIH-severity scoring system). [56] A recent systematic review found high heterogeneity in use of scoring system and concluded that the lack of standardized indices potentially accounts for the high variability of prevalence reports and highlights the difficulty in comparing studies to develop an evidence-based guideline for MIH optimal management. [6]

3. EVIDENCE-BASED TREATMENT STRATEGIES

In children affected with MIH treatment is very challenging as not only the need is amplified but also achieving a highly satisfactory restoration of affected teeth long-term is required. By the age of nine children with MIH will require ten times more dental treatment compared to children with unaffected teeth with each affected tooth reportedly requires at least two treatment. [57] Moreover, management strategies are further complicated due to limited evidence for correlation between clinical presentation of the affected enamel with severity of MIH. [58] As a result, a broad spectrum of treatment modalities has been produced to address such differences including products for preventive or restorative treatment. [4, 8, 35] Furthermore, differential diagnosis is mandatory to exclude other dental conditions such as amelogenesis (or dentinogenesis) imperfecta, enamel hypoplasia and fluorosis. Collaboration between pediatricians and pediatric dentists is essential to reach an early diagnosis and achieve long-term satisfactory treatment outcomes for a healthier and happier child. [21, 59].

Depending on the severity of MIH a range of treatments have been found to be effective with longitudinal studies reporting their long-term success. Table 2 summarizes the evidence collected from recent systematic reviews on treatment modalities reported for children affected with MIH condition.

3.1 Preventive measures

Implementation of preventive measures following MIH diagnosis needs to be individually tailored and considered in light of collaborative efforts and patient factors including age, caries risk, hypersensitivity level as well as type and severity of the demarcated lesions. [53] Both initial risk assessment and early diagnosis are the key factors for an effective and conservative management of patients affected with MIH. The initial management phase should also include administration of remineralizing agent to affected teeth immediately after MIH diagnosis. [60]

3.1.1 Desensitizing agents

Several agents have been developed to address hypomineralized teeth issues. Bekes and colleagues [61] showed a significant reduction in hypersensitivity by applying an arginine paste to MIH affected teeth. The underlying mechanism involves stimulation of dentinal tubule obliteration by arginine thereby abolishing hydrodynamic pain activity. Following twice daily application of an arginine desensitizing paste on affected teeth for 8 weeks a considerable decrease in hypersensitivity was reported. [62-63] In clinic application of fluoride varnish as a desensitizing agent has also been found to alleviate dental hypersensitivity. [64-65] Further support of these clinical studies comes from a recent systematic review that showed the most effective preventive measures to reduce hypersensitivity were reported to be use of arginine pastes or fluoride varnishes. [66].

3.1.2 Sedative interim restorations

Interim restorations are feasible solution when it is not possible to achieve total comfort for the child during treatment. [67] Glass ionomers have been the gold standard interim restorative material for decades due to their sedative properties for hypersensitivity management. [68] A two-step procedure maybe applied during treatment to ensure the comfort of the child: The restorative procedure can be stopped and a sedative filling as an interim restoration

Table 1. Summary of evidence from systematic reviews and meta-analyses during last 10 years relate to prevalence, diagnosis and etiological factors in children affected with MIH

Study (year)	Study design	Focus of study	Studies identified	Findings	Conclusions
Wu et al. [43]	SR and MA	Etiology	SR: 17 studies MA: 4 studies	MIH 3 times more prevalent in low birth-weight neonates (OR=3.25, 95%CI: 2.28–4.62) MIH showed 1.6 times higher association with premature birth (OR=1.57, 95%CI: 1.07–2.31)	MIH was higher association with premature birth and low birth weight
Fatturi et al. [39]	SR and MA	Systemic exposure	SR: 29 studies MA: 27 studies	The following were associated with higher prevalence of MIH: Maternal illness during pregnancy (OR 1.40; 95% CI 1.18-1.65, P < 0.0001) psychological stress (OR = 2.65; 95% CI 1.52-4.63; P = 0.001) caesarean delivery (OR = 1.32, 95% CI 1.11-1.57, P = 0.001) delivery complications (OR = 2.06; 95% CI 1.47-2.88, P < 0.0001) respiratory diseases (OR = 1.98; 95% CI 1.45-2.70, P < 0.0001) fever (OR = 1.50; 95% CI 1.22-1.84; P < 0.0001)	During early life, MIH was highly associated with maternal illness, psychological stress, caesarean delivery & complications, respiratory diseases as well as fever. Since studies were heterogenous and observational, findings should be interpreted with caution.
Americano et al.(2017)	SR	Caries	17 controlled-clinical studies	DMF index and caries prevalence were Higher in children with MIH than in children without MIH	significant association between MIH and dental caries
Pentapati et al. (2017)	SR and MA	Prevalence	61 studies	Lower prevalence in Asia compared with Europe and South America In more than half of studies MIH wasHigher in girls than boys	MIH prevalence is 11% and varied geographically with mild variation in genders.
Serna et al. [42]	SR	Systemic exposure	20 studies	Evidence for MIH associated with the following not sufficient: chemotherapeutic, antibiotics, asthma, antiepileptic, antiviral And antifungal drugs	Association between MIH and medication use is not sufficiently supported
Silva et al. [40]	SR	Etiology	25 MIH 3 HSPM human studies	Limited associations: Prenatal factors such as maternal smoking, illness & medication use perinatal factors: low birthweight, prematurity and birth complications Significant association: Early childhood illness including fever asthma and pneumonia	MIH: considerable association with early childhood illness HSPM: significant association with maternal alcohol intake
Alaluusua [41]	SR	Etiology	28 MIH human & animal studies	Association with fever, hypocalcemia hypoxia & amoxicillin	Although correlation was found between MIH and putative factors including high fever, hypoxia and antibiotics, higher level of evidence required to verify multifactorial etiology
Jälevik [7]	SR	Prevalence & Diagnosis	24 MIH human studies	Inconsistent use of MIH criteria, variable examination and recording	For cross-comparison study designs and reporting need to be standardization

Abbreviations. HSPM: hypomineralized second primary molars; Meta; Meta-analysis

Table 2. Summary of evidence from systematic reviews and a meta-analysis on treatment modalities for children affected with MIH

Study (year)	Study design	Aim of study [Focus]	Studies identified	Follow-up (months)	Findings	Conclusions
Lagrade et al. (2020)	SR	Identify best bonding protocols [Restorative]	4 clinical studies 2	3 to 24 months	No difference noted between self-etch and etch-rinse adhesives Use of deproteinization following etch-rinse enhanced bond strength. Sealant studies were inconclusive	Due to the heterogeneity of MIH severity and adhesives used definitive conclusions cannot be drawn
Coelho et al. (2019)	SR	Effectiveness of treatment interventions [Restorative & preventive]	12 clinical studies 1 (Both Molar and Incisors)	1 to 48 months	Treatments reported: Use of remineralizing products, resin infiltration, restorations, fissure sealants	Most effective treatments: arginine pastes or fluoride varnishes
Elhennawy et al. [69]	SR & SNA	outcome and comparator choice [All outcomes]	28 clinical 7 clinical 3 studies (Total 35 clinical studies)	1 -99 m 1-6 m 3	11 outcomes reported related to: Restoration, hypersensitivity/pain, esthetic, effectiveness of anesthesia space management, prevention, mineral gain, quality of life, periodontal health, costs, & patient satisfaction. Comparators were restorative interventions, remineralization, hypersensitivity treatment, aesthetic and orthodontic interventions.	Most primary outcomes: restoration success & pain management The limited number of studies reporting a wide range of outcomes indicates evidence is not robust
Elhennawy et al. (2016)	SR	Identify MIH treatments and evaluate their performance [Restorative & preventive]	10 clinical 4 clinical 3 studies (Total 14 clinical studies)	12-99 m 1-30 m 3	Restorative failures: 12% fissure sealants, 12% glass-ionomer, 4% composite restorations. For hypersensitivity desensitizing agents were applied with 81% success after 1 month	Most studies were observational and not controlled. Treatment indication should be based on MIH severity and hypersensitivity
Lygidakis [8]	SR	Review literature on MIH treatment [Restorative]	14 clinical studies		Treatment of choice for mild-moderate MIH: composite Severe MIH: case by case	Limited clinical trials found. Long-term clinical trials supported by laboratory Studies required

1 Other studies were on dental fluorosis (21 studies. 2 Also 6 laboratory studies, 3 studies reporting on incisors affect by MIH; Abbreviations. SNA: social network analysis;

administered to help soothe the highly reactive tooth. After 1-2 weeks, the restorative procedure can be revisited with now a more easily anesthetized tooth and a more successful definitive restoration placed. This could particularly be a useful strategy in shorter and more comfortable appointments that allow younger patient to cooperate better.[60] Recent evidence from clinical studies has also shown glass ionomer to have a low failure rate as a restorative material over three years. [69].

3.1.3 Fissure sealants

These preventive measures are considered one of the most effective and successful treatments of MIH teeth. [67] Lygidakis and colleagues [70] reported that fissure sealant application using a two-step (etch-and-rinse) adhesive system had a higher retention rate than sealants without application of an etch. In addition, the retention of a resin-based sealant in hypomineralized molars was significantly higher than use of a glass ionomer sealant. [71]

3.2 Restorative Measures

3.2.1 Resin composites

Although the evidence for the use of self-etch and etch-rinse adhesives with composite resin indicates no difference in terms of effectiveness for treatment of MIH teeth, nevertheless due to diverse reports in adhesives and techniques definitive conclusions cannot be reached.72 Studies have found that the success rate of resin self-etch or total-etch adhesives is considerably lower at 18 months [73] likely due to the enamel defect that compromises the successful adhesion of the resin to the affected dental surface. [51, 74] However, Sönmez and Saat showed that following removal of the entire affected enamel, restoration of the hypomineralized teeth with a resin composite was highly successful when compared to restorations with limited removal of clinically defective enamel tissue.75 In addition, two coats of adhesive would be required for long-term success of the restoration since the porous hypomineralized surface in MIH absorbs the first adhesive coating. [76].

3.2.2 Resin infiltration

The application of resin infiltrate in arresting non-cavitated carious lesions has been recently demonstrated. [77] However icon infiltration in MIH-affected enamel has been only evaluated in experimental studies [72] and further research is required to explore this technique on clinically hypomineralized enamels.

3.2.3 Amalgam restorations

Since amalgam is a non-adhesive restorative material
and placement of mechanical retention further weakens the tooth structure, therefore it is best to be avoided in these atypically shaped cavities. [78]

3.3 Esthetic Measures

3.3.1 Bleaching for esthetics

The use of hydrogen peroxide or carbamide peroxide formulations administered at different bleaching concentrations resulted in esthetic improvement in all cases with MIH. [66].

3.3.2 Microabrasion for esthetics

This is a minimally invasive technique which involves removal of external enamel surface defects via an abrasion and chemical erosion (18% hydrochloric acid) technique. The limitation of this technique is that treatment success depends on the depth of the discoloration. Moreover, this procedure should be limited to more superficial enamel defects with deeper defects benefiting from additional treatment measures. [79-80] For improved esthetic outcomes in mild to moderate cases of MIH, the enamel microabrasion technique maybe combined with dental bleaching. [79, 81].

3.3.3 Deproteinization

Application of a 5% sodium hypochlorite solution following acid conditioning has been found to be ideal for deproteinization. Bond strength can be achieved after deproteinization without removal of the defected enamel surfaces. However, further research is required to evaluate the clinical effectiveness of this technique. [72, 75, 82].

3.3.4 Full coverage

Stainless steel crowns are ideal interim solution in younger patients who experience severe form of hypomineralized molars to protect the remaining tooth structure from early breakdown, relief hypersensitivity and establish plaque-free interproximal and occlusal contacts. In case of

crown cementation in incomplete tooth eruption, glass-ionomer cement is the ideal material to be considered. [83-85]

3.4 Other Measures

3.4.1 Extraction and orthodontics

Extraction of a first permanent molars (FPM) is not ideal functionally nor it is an orthodontist's first choice for malocclusion correction. However, in case of poor long-term prognosis, best age to perform extraction of these teeth is usually before the age of 8.5-9 years. Radiographically, once the mandibular permanent second molar shows signs of calcification of bifurcation then extraction option should be considered. This will encourage forward movement of permanent second molars into a good alignment. If the mandibular FPM is extracted, then maxillary FPM should be considered as a compensation. [78, 86-87]

4. CONCLUSION

MIH is considered a significant dental public health concern globally. Early diagnosis by all clinicians involved in oral health management of children facilitates optimal treatment implementation as well as improved quality of life of affected children and their families. The esthetics of MIH is the most challenging aspect of its management and treatment should be tailored to address the needs of the child, to prevent loss of further tooth structure and caries development for as long as possible. This entails combining treatment as an esthetic and functional rehabilitation and to treat dental hypersensitivity where required. Therefore, importance of both short and long-term approaches to treatment planning with regular dental visits needs to be communicated to the parents for optimal clinical management and improved prognosis of MIH in affected children.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Seow W. Developmental defects of enamel and dentine: challenges for basic science research and clinical management. Australian Dental Journal. 2014;59:143-154.
2. Vieira LDS, Paschoal MAB, de Barros Motta P, Ferri EP, Ribeiro C, Dos Santos-Pinto LAM, Motta LJ, Goncalves MLL, Horliana A, Fernandes KPS, Ferrari RAM, Deana AM, Bussadori SK. Antimicrobial photodynamic therapy on teeth with molar incisor hypomineralization-controlled clinical trial. Medicine. 2019;98(39): e17355.
3. Weerheijm KL, Jalevik B, Alaluusua S, Molar-incisor hypomineralisation. Caries Research. 2001;35 (5):390-1.
4. Weerheijm KL, Duggal M, Mejare I, Papagiannoulis L, Koch G, Martens LC, Hallonsten AL. Judgement criteria for molar incisor hypomineralisation (MIH) in epidemiologic studies: a summary of the European meeting on MIH held in Athens. European journal of paediatric dentistry 2003;4(3):110-3.
5. Weerheijm KL. Molar incisor hypomineralisation (MIH). European Journal of Paediatric Dentistry 2003;4 (3):114-20.
6. Allam E, Ghoneima A, Kula K. Defi nition and scoring system of molar incisor hypomineralization: A review. Dent Oral Craniofac Res. 2017;3:1-9.
7. Jälevik B. Prevalence and diagnosis of molar-incisor-hypomineralisation (MIH): a systematic review. European Archives of Paediatric Dentistry. 2010;11(2):59-64.
8. Lygidakis NA, Wong F, Jälevik B, Vierrou AM, Alaluusua S, Espelid I. Best Clinical Practice Guidance for clinicians dealing with children presenting with Molar-Incisor-Hypomineralisation (MIH): An EAPD Policy Document. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry. 2010;11(2):75-81.
9. Garot E, Denis A, Delbos Y, Manton D, Silva M, Rouas P. Are hypomineralised lesions on second primary molars (HSPM) a predictive sign of molar incisor hypomineralisation (MIH)? A systematic review and a meta-analysis. Journal of Dentistry. 2018;72:8-13.
10. Solanki HP, Mathur A, Kamath A, Patil V. Influence of Deciduous Molar

Hypomineralization on Molar Incisor Hypomineralization–A Systematic Review. Indian Journal of Public Health Research & Development. 2020;11(6):1154-1159.
11. Reyes MRT, Fatturi AL, Menezes J, Fraiz FC, Assunção L, Souza JF. Demarcated opacity in primary teeth increases the prevalence of molar incisor hypomineralization. Brazilian Oral Research. 2019;33:e048.
12. Balmer R, Toumba KJ, Munyombwe T, Godson J, Duggal MS. The prevalence of incisor hypomineralisation and its relationship with the prevalence of molar incisor hypomineralisation. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry. 2015;16(3):265-9.
13. Ghanim A, Elfrink M, Weerheijm K, Mariño R, Manton D. A practical method for use in epidemiological studies on enamel hypomineralisation. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry. 2015;16 (3):235-46.
14. Curzon ME, Ogden AR, Williams-Ward M, Cleaton-Jones PE. Case report: A medieval case of molar-incisor-hypomineralisation. British Dental Journal. 2015;219(12):583-7.
15. Koch G, Hallonsten AL, Ludvigsson N, Hansson BO, Holst A, Ullbro C. Epidemiologic study of idiopathic enamel hypomineralization in permanent teeth of Swedish children. Community Dentistry and Oral Epidemiology. 1987;15(5):279-85.
16. Zhao D, Dong B, Yu D, Ren Q, Sun Y. The prevalence of molar incisor hypomineralization: evidence from 70 studies. International Journal of Paediatric Dentistry. 2018;28 (2):170-179.
17. Denis M, Atlan A, Vennat E, Tirlet G, Attal JP. White defects on enamel: diagnosis and anatomopathology: two essential factors for proper treatment (part 1). International orthodontics 2013;11(2):139-65.
18. Kukleva MP, Petrova SG, Kondeva VK, Nihtyanova TI. Molar incisor hypomineralisation in 7-to-14-year old children in Plovdiv, Bulgaria--an epidemiologic study. Folia medica. 2008;50(3):71-5.
19. Dietrich G, Sperling S, Hetzer G. Molar incisor hypomineralisation in a group of children and adolescents living in Dresden (Germany). European Journal of Paediatric Dentistry. 2003;4(3):133-7.
20. Cho SY, Ki Y, Chu V. Molar incisor hypomineralization in Hong Kong Chinese children. International Journal of Paediatric Dentistry. 2008;18(5):348-52.
21. Glodkowska N, Emerich K. Molar Incisor Hypomineralization: prevalence and severity among children from Nothern Poland. European Journal of Paediatric Dentistry. 2019;20(1):59-66.
22. Silva MJ, Alhowaish L, Ghanim A, Manton DJ. Knowledge and attitudes regarding molar incisor hypomineralisation amongst Saudi Arabian dental practitioners and dental students. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry 2016;17 (4):215-22.
23. Sidhu N, Wang Y, Barrett E, Casas M. Prevalence and presentation patterns of enamel hypomineralisation (MIH and HSPM) among paediatric hospital dental patients in Toronto, Canada: a cross-sectional study. European Archives of Paediatric Dentistry : Official Journal of the European Academy of Paediatric Dentistry;2019.
24. Kemoli AM. Prevalence of molar incisor hypomineralisation in six to eight year-olds in two rural divisions in Kenya. East African Medical Journal. 2008;85(10):514-9.
25. Schmalfuss A, Stenhagen KR, Tveit AB, Crossner CG, Espelid I. Canines are affected in 16-year-olds with molar-incisor hypomineralisation (MIH): an epidemiological study based on the Tromsø study: "Fit Futures". European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry. 2016;17(2):107-13.
26. Alaluusua S, Lukinmaa PL, Koskimies M, Pirinen S, Hölttä P, Kallio M, Holttinen T, Salmenperä L. Developmental dental defects associated with long breast feeding. European Journal of Oral Sciences. 1996;104(5-6):493-7.
27. Praptiwi YH, Prayitno ND, Sukmasari S. Prevalence of Molar Incisors Hypomineralisation (MIH) in primary school children. Padjadjaran Journal of Dentistry. 2019;31(2):79-84.
28. Hussain G, Al-Halabi M, Kowash M, Hassan A. The Prevalence and Severity of Molar Incisor Hypomineralization and Molar Hypomineralization in Dubai, UAE.

Journal of dentistry for children (Chicago, Ill.) 2018;85 (3):102-107.
29. Masumo R, Bårdsen A, Astrøm AN. Developmental defects of enamel in primary teeth and association with early life course events: a study of 6-36 month old children in Manyara, Tanzania. BMC oral health. 2013;13:21.
30. Wogelius P, Haubek D, Poulsen S. Prevalence and distribution of demarcated opacities in permanent 1st molars and incisors in 6 to 8-year-old Danish children. Acta odontologica Scandinavica. 2008;66(1):58-64.
31. Soviero V, Haubek D, Trindade C, Da Matta T, Poulsen S. Prevalence and distribution of demarcated opacities and their sequelae in permanent 1st molars and incisors in 7 to 13-year-old Brazilian children. Acta odontologica Scandinavica. 2009;67(3):170-5.
32. Giuca MR, Cappè M, Carli E, Lardani L, Pasini M. Investigation of Clinical Characteristics and Etiological Factors in Children with Molar Incisor Hypomineralization. International journal of dentistry. 2018;7584736.
33. Beentjes VE, Weerheijm KL, Groen HJ. Factors involved in the aetiology of molar-incisor hypomineralisation (MIH). European Journal of Paediatric Dentistry. 2002;3(1):9-13.
34. Crombie F, Manton D, Kilpatrick N. Aetiology of molar-incisor hypomineralization: a critical review. International Journal of Paediatric Dentistry. 2009;19(2):73-83.
35. Weerheijm KL. Molar incisor hypomineralization (MIH): clinical presentation, aetiology and management. Dental update. 2004;31(1):9-12.
36. Weerheijm KL, Groen HJ, Beentjes VE, Poorterman JH. Prevalence of cheese molars in eleven-year-old Dutch children. ASDC Journal of Dentistry for Children. 2001;68(4):259-62.
37. Tourino LF, Corrêa-Faria P, Ferreira RC, Bendo CB, Zarzar PM, Vale MP. Association between Molar Incisor Hypomineralization in Schoolchildren and Both Prenatal and Postnatal Factors: A Population-Based Study. PloS one. 2016;11(6):e0156332.
38. Akcam MO, Toygar TU, Ozer L, Ozdemir B. Evaluation of 3-dimensional tooth crown size in cleft lip and palate patients. American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 2008;134(1):85-92.
39. Fatturi AL, Wambier LM, Chibinski AC, Assunção L, Brancher JA, Reis A, Souza JF. A systematic review and meta-analysis of systemic exposure associated with molar incisor hypomineralization. Community dentistry and oral epidemiology. 2019;47(5):407-415.
40. Silva MJ, Scurrah KJ, Craig JM, Manton DJ, Kilpatrick N. Etiology of molar incisor hypomineralization - A systematic review. Community dentistry and oral epidemiology. 2016;44(4): 342-53.
41. Alaluusua S. Aetiology of Molar-Incisor Hypomineralisation: A systematic review. European Archives Of Paediatric Dentistry : Official Journal of the European Academy of Paediatric Dentistry 2010;11(2):53-8.
42. Serna C, Vicente A, Finke C, Ortiz AJ. Drugs related to the etiology of molar incisor hypomineralization: a systematic review. The Journal of the American Dental Association. 2016; 147 (2):120-130.
43. Wu X, Wang J, Li YH, Yang ZY, Zhou Z. Association of molar incisor hypomineralization with premature birth or low birth weight: systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2020;33(10):1700-1708.
44. Elhennawy K, Krois J, Jost-Brinkmann PG, Schwendicke F. Outcome and comparator choice in molar incisor hypomineralisation (MIH) intervention studies: a systematic review and social network analysis. BMJ Open. 2019;9(8):e028352.
45. Vieira AR, Kup E. On the Etiology of Molar-Incisor Hypomineralization. Caries research. 2016;50 (2):166-9.
46. Kühnisch J, Thiering E, Heitmüller D, Tiesler CM, Grallert H, Heinrich-Weltzien R, Hickel R, Heinrich J. Genome-wide association study (GWAS) for molar-incisor hypomineralization (MIH). Clinical oral investigations. 2014;18 (2):677-82.
47. Jeremias F, Koruyucu M, Kuchler EC, Bayram M, Tuna EB, Deeley K, Pierri RA, Souza JF, Fragelli CM, Paschoal MA, Gencay K, Seymen F, Caminaga RM, dos Santos-Pinto L, Vieira AR. Genes expressed in dental enamel development are associated with molar-incisor hypomineralization. Archives of oral biology. 2013;58(10):1434-42.

48. Shimizu T, Ho B, Deeley K, Briseno-Ruiz J, Faraco IM, Jr. Schupack BI, Brancher JA, Pecharki GD, Kuchler EC, Tannure PN, Lips A, Vieira TC, Patir A, Yildirim M, Poletta FA, Mereb JC, Resick JM, Brandon CA, Orioli IM, Castilla EE, Marazita ML, Seymen F, Costa MC, Granjeiro JM, Trevilatto PC, Vieira AR. Enamel formation genes influence enamel microhardness before and after cariogenic challenge. PloS one. 2012;7 (9):e45022.
49. Caruso S, Bernardi S, Pasini M, Giuca MR, Docimo R, Continenza MA, Gatto R. The process of mineralisation in the development of human tooth. European Journal of Paediatric Dentistry. 2016; 17 (4):322-326.
50. Tannure PN, Oliveira CA, Maia LC, Vieira AR, Granjeiro JM, Costa Mde C. Prevalence of dental anomalies in nonsyndromic individuals with cleft lip and palate: a systematic review and meta-analysis. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association. 2012;49 (2):194-200.
51. Fagrell TG, Dietz W, Jälevik B, Norén JG. Chemical, mechanical and morphological properties of hypomineralized enamel of permanent first molars. Acta odontologica Scandinavica. 2010;68(4): 215-22.
52. Neves AB, Americano GCA, Soares DV, Soviero VM. Breakdown of demarcated opacities related to molar-incisor hypomineralization: a longitudinal study. Clinical oral investigations. 2019;23(2): 611-615.
53. Giuca MR, Lardani L, Pasini M, Beretta M, Gallusi G, Campanella V. State-of-the-art on MIH. Part. 1 Definition and aepidemiology. European Journal of Paediatric Dentistry. 2020;21(1):80-82.
54. Fteita D, Ali A, Alaluusua S. Molar-incisor hypomineralization (MIH) in a group of school-aged children in Benghazi, Libya. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry. 2006;7(2):92-5.
55. Whatling R, Fearne JM. Molar incisor hypomineralization: a study of aetiological factors in a group of UK children. International Journal of Paediatric Dentistry. 2008;18(3):155-62.
56. Cabral RN, Nyvad B, Soviero V, Freitas E, Leal SC. Reliability and validity of a new classification of MIH based on severity. Clinical Oral Investigations. 2020;24(2): 727-734.
57. Jalevik B, Klingberg GA. Dental treatment, dental fear and behaviour management problems in children with severe enamel hypomineralization of their permanent first molars. International Journal of Paediatric Dentistry. 2002;12(1):24-32.
58. Elhennawy K, Manton DJ, Crombie F, Zaslansky P, Radlanski RJ, Jost-Brinkmann PG, Schwendicke F. Structural, mechanical and chemical evaluation of molar-incisor hypomineralization-affected enamel: A systematic review. Archives of Oral Biology. 2017;83:272-281.
59. Paglia L. Molar Incisor Hypomineralization: paediatricians should be involved as well! European Journal of Paediatric Dentistry. 2018;19(3):173.
60. William V, Messer LB, Burrow MF. Molar incisor hypomineralization: review and recommendations for clinical management. Pediatric Dentistry. 2006;28(3):224-32.
61. Bekes K, Heinzelmann K, Lettner S, Schaller HG. Efficacy of desensitizing products containing 8% arginine and calcium carbonate for hypersensitivity relief in MIH-affected molars: an 8-week clinical study. Clinical oral investigations. 2017:21(7):2311-2317.
62. Sharif MO, Iram S, Brunton PA. Effectiveness of arginine-containing toothpastes in treating dentine hypersensitivity: a systematic review. Journal of Dentistry. 2013;41(6):483-92.
63. Yang ZY, Wang F, Lu K, Li YH, Zhou Z. Arginine-containing desensitizing toothpaste for the treatment of dentin hypersensitivity: a meta-analysis. Clinical, Cosmetic and Investigational Dentistry. 2016;8:1-14.
64. Restrepo M, Jeremias F, Santos-Pinto L, Cordeiro RC, Zuanon AC. Effect of Fluoride Varnish on Enamel Remineralization in Anterior Teeth with Molar Incisor Hypomineralization. The Journal of Clinical Pediatric Dentistry. 2016;40(3):207-10.
65. Ozgül BM, Saat S, Sönmez H, Oz FT. Clinical evaluation of desensitizing treatment for incisor teeth affected by molar-incisor hypomineralization. The Journal of Clinical Pediatric Dentistry. 2013;38 (2):101-5.
66. Da Cunha Coelho ASE, Mata PCM, Lino CA, Macho VMP, Areias C, Norton A, Augusto A. Dental hypomineralization

treatment: A systematic review. Journal of esthetic and restorative dentistry : official publication of the American Academy of Esthetic Dentistry. 2019;31(1):26-39.
67. Fragelli CMB, Souza JF, Bussaneli DG, Jeremias F, Santos-Pinto LD, Cordeiro RCL. Survival of sealants in molars affected by molar-incisor hypomineralization: 18-month follow-up. Brazilian oral Research. 2017;31:e30.
68. Hansen EK. Dentin hypersensitivity treated with a fluoride-containing varnish or a light-cured glass-ionomer liner. Scandinavian Journal of Dental Research. 1992;100(6):305-9.
69. Elhennawy K, Schwendicke F. Managing molar-incisor hypomineralization: A systematic review. Journal of Dentistry. 2016;55:16-24.
70. Lygidakis NA, Dimou G, Stamataki E. Retention of fissure sealants using two different methods of application in teeth with hypomineralised molars (MIH): a 4 year clinical study. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry. 2009;10 (4):223-6.
71. Hasanuddin S, Reddy ER, Manjula M, Srilaxmi N, Rani ST, Rajesh A. Retention of fissure sealants in young permanent molars affected by dental fluorosis: a 12-month clinical study. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry 2014;15(5):309-15.
72. Lagarde M, Vennat E, Attal JP, Dursun E. Strategies to optimize bonding of adhesive materials to molar-incisor hypomineralization-affected enamel: A systematic review. International journal of Paediatric Dentistry;2020.
73. De Souza JF, Fragelli CB, Jeremias F, Paschoal MAB, Santos-Pinto L, de Cássia Loiola Cordeiro, R. Eighteen-month clinical performance of composite resin restorations with two different adhesive systems for molars affected by molar incisor hypomineralization. Clinical oral investigations. 2017; 21(5):1725-1733.
74. William V, Burrow MF, Palamara JE, Messer LB. Microshear bond strength of resin composite to teeth affected by molar hypomineralization using 2 adhesive systems. Pediatric Dentistry. 2006;28 (3):233-41.
75. Sönmez H, Saat S. A Clinical Evaluation of Deproteinization and Different Cavity Designs on Resin Restoration Performance in MIH-Affected Molars: Two-Year Results. The Journal of clinical Pediatric Dentistry. 2017;41(5):336-342.
76. Ekambaram M, Anthonappa RP, Govindool SR, Yiu CKY. Comparison of deproteinization agents on bonding to developmentally hypomineralized enamel. Journal of Dentistry. 2017;67:94-101.
77. Gugnani N, Pandit IK, Gupta M, Gugnani S, Soni S, Goyal V. Comparative evaluation of esthetic changes in nonpitted fluorosis stains when treated with resin infiltration, in-office bleaching, and combination therapies. Journal of esthetic and restorative dentistry : official publication of the American Academy of Esthetic Dentistry ... [et al.] 2017;29(5):317-324.
78. Willmott NS, Bryan RA, Duggal MS. Molar-incisor-hypomineralisation: a literature review. European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry 2008;9 (4):172-9.
79. Pini NI, Sundfeld-Neto D, Aguiar FH, Sundfeld RH, Martins LR, Lovadino JR, Lima DA. Enamel microabrasion: An overview of clinical and scientific considerations. World journal of clinical cases 2015;3(1):34-41.
80. Bassir MM, Bagheri G. Comparison between phosphoric acid and hydrochloric acid in microabrasion technique for the treatment of dental fluorosis. Journal of conservative dentistry: JCD 2013;16(1):41-4.
81. Farid H, Khan FR. Clinical management of severe fluorosis in an adult. BMJ case reports;2012.
82. Gandhi S, Crawford P, Shellis P. The use of a 'bleach-etch-seal' deproteinization technique on MIH affected enamel. International journal of paediatric dentistry. 2012;22(6):427-34.
83. Daly D, Waldron JM. Molar incisor hypomineralisation: clinical management of the young patient. Journal of the Irish Dental Association. 2009;55(2):83-6.
84. Mast P, Rodrigueztapia MT, Daeniker L, Krejci I. Understanding MIH: definition, epidemiology, differential diagnosis and new treatment guidelines. European Journal of Paediatric Dentistry. 2013; 14(3):204-8.
85. Fayle SA. Molar incisor hypomineralisation: restorative

management. European Journal of Paediatric Dentistry. 2003;4(3):121-6.

86. Williams JK, Gowans AJ. Hypomineralised first permanent molars and the orthodontist. European journal of paediatric dentistry 2003;4(3):129-32.

87. Eichenberger M, Erb J, Zwahlen M, Schätzle M. The timing of extraction of non-restorable first permanent molars: a systematic review. European Journal of Paediatric Dentistry. 2015;16(4): 272-8.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/75299