Journal of Dentistry 55 (2016) 16–24

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.intl.elsevierhealth.com/journals/jden

Review article

Managing molar-incisor hypomineralization: A systematic review

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ARTICLE INFO

Article history:
Received 9 June 2016
Received in revised form 22 September 2016
Accepted 27 September 2016

Keywords:
Dental
Developmental defects
Evidence-based dentistry
Hypoplasia
MIH

ABSTRACT

Objectives: We systematically reviewed treatment modalities for MIH-affected molars and incisors.
Data: Trials on humans with ≥1 MIH molar/incisor reporting on various treatments were included. Two authors independently searched and extracted records. Sample-size-weighted annual failure rates were estimated where appropriate. The risk of bias was assessed using the Newcastle-Ottawa scale.
Sources: Electronic databases (PubMed, Embase, Cochrane CENTRAL, Google Scholar) were screened, and hand searches and cross-referencing performed.
Study selection: Fourteen (mainly observational) studies were included. Ten trials (381 participants) investigated MIH-molars, four (139) MIH-incisors. For molars, remineralization, restorative or extraction therapies had been assessed. For restorative approaches, mean (SD) annual failure rates were highest for fissure sealants (12[6]%) and glass-ionomer restorations (12[2]%), and lowest for indirect restorations (1 [3]%), preformed metal crowns (1.3 [2.1]%) and composite restorations (4[3]%). Ony study assessed extraction of molars in young patients (median age 8.2 years), the majority of them without malocclusions, but third molars in development. Spontaneous alignment of second molars was more frequent in the maxilla (55%) than the mandible (47%). For incisors, desensitizing agents successfully managed hypersensitivity. Micro-abrasion and composite veneers improved aesthetics.
Conclusions: Few, mainly moderate to high-risk-studies investigated treatment of MIH. Remineralization or sealants seem suitable for MIH-molars with limited severity and/or hypersensitivity. For severe cases, restorations with composites or indirect restorations or preformed metal crowns seem suitable. Prior to tooth extraction as last resort factors like the presence of a general malocclusion, patients' age and the status of neighboring teeth should be considered. No recommendations can be given for MIH-incisors.
Clinical significance: Dentists need to consider the specific condition of each tooth and the needs and expectations of patients when deciding how to manage MIH. Strong recommendations are not possible based on the current evidence.

1. Introduction

Non-endemic mottling of enamel, internal enamel hypoplasia, cheese molars, non-fluoride enamel opacities, idiopathic enamel spots or opacities are all different terms used to describe the condition currently known as molar-incisor hypomineralization (MIH) [1]. MIH is defined as demarcated, qualitative developmental defects of systemic origin of the enamel of one or more permanent first molar with or without the affection of incisors [2–4]. The clinical characteristics of MIH vary both between and within patients [2,3]. The prevalence of MIH is relatively high, and is reported to range from 3 to 22% in Europe [5–7].

A number of etiological hypotheses for MIH have been postulated. Prenatal exposures (like maternal smoking or illness during pregnancy), perinatal exposures (like premature or prolonged birth, low birth weight, cesarean delivery, and birth complications) and postnatal exposures (like early childhood illness or medication or breastfeeding) are discussed as being causative or associated with MIH. In any case, multifactorial pathogenesis with a possible genetic component seems likely [8–12].

In comparison to normal teeth, MIH-affected teeth show histologically less distinct prism sheaths and a lack of arrangement of the enamel crystals. The hypomineralized enamel shows lower mechanical properties, as hardness and modulus of elasticity were

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http://dx.doi.org/10.1016/j.jdent.2016.09.012
0300-5712/

found to have lower values than those found in normal enamel [13–18]. MIH enamel shows increased amounts of proteins like serum albumin, type I collagen, ameloblastin, α1-antitrypsin, and antithrombin III, which were found to inhibit the growth of hydroxyapatite crystals and enzymatic activity during enamel maturation, resulting in an overall reduction of minerals in MIH enamel [19,20].

The management of MIH is challenging as the clinical appearance and individual need for treatment varies widely, with a broad spectrum of treatment modalities being available, ranging from prevention of enamel breakdown or caries, management of hypersensitivity or pain, restorative treatments, to extraction with or without subsequent orthodontic alignment of adjacent teeth [2–4]. The decision as to which of these options is suitable needs to be made individually considering the severity of the lesions, the symptomatology of the affected tooth as well as the patient's dental age and expectations [3]. Moreover, knowledge on the suitability of different treatments for specific situations as to their success (no need for re-intervention), survival (no need to extract MIH-affected molars), subjective evaluation (absence of postoperative mild or severe pain, aesthetics, and masticatory function) and cost-effectiveness is needed to make informed clinical decisions.

A number of reviews have reported on available treatment modalities; with one exception all these reviews have not been performed systematically [3]. A systematic review of treatment modalities in MIH-affected molars and incisors is needed to inform practitioners as to how well different treatments perform in different patients, and to guide future research in the direction of MIH treatment. We aimed to answer the following question: In children diagnosed with MIH, which treatments have been evaluated by clinical studies, and how did these treatments perform?

2. Methods

2.1. Eligibility criteria

This systematic review (registered at PROSPERO CRD42016039677) included clinical trials

- on human subjects having a minimum of one permanent first molar with MIH (with or without affection of one or more incisor) in need of any, i.e. preventive, restorative, endodontic, surgical and/or orthodontic, treatment. Note that the decision as to if a treatment was needed could have been made subjectively; we did not predefine criteria how such need was decided. Given the wide range of treatment modalities, we expected a range of lesion severities and symptomatologies to be included.
- reporting on minimum one such treatment, which means that studies could be retrospective or prospective, controlled trials or cohort studies.
- with a minimum sample size of 10 to exclude small case series, as any inference as to how well a treatment truly performs based on such small sample sizes is unlikely to be robust
- reporting on the "performance" of the provided treatment, as described below.

Consequently, case reports or small case series, studies describing a treatment method without reporting any results, review articles or non-clinical studies were excluded.

2.2. Outcomes

The primary outcome was the "success" of a treatment, i.e. the proportion of teeth and/or patients where the treatment did not need repeating or other re-interventions. Success captures a range of complications, like enamel breakdown, caries occurrence, restoration failure, pain needing endodontic treatment, or the proportion of cases requiring orthodontic alignment after extraction (i.e. without spontaneous alignment).

Preventive treatments, like fluoride varnishes, are oftentimes repeated in a planned manner without this being considered a "failure". Therefore, success was defined as the proportion of teeth or patients, which did not require further (restorative, endodontic, surgical) interventions for these treatments.

The secondary outcomes were

- adverse events (like allergies towards a used material)
- treatment costs or efforts (required time, materials)
- subjective evaluations by patients, parents, or dentists.

We have not specified upfront how outcomes needed to be reported (on binary, ordinal or continuous scale etc.).

2.3. Information sources and study selection

We searched Medline via PubMed, Embase via Ovid, Cochrane Central and Google Scholar. Moreover, opengrey.eu was searched to identify accepted, but not published studies. In addition, reference lists of identified full texts were screened and cross-referenced. We contacted study authors if required to obtain full texts. The search covered a period from January 1, 1980, to May 1, 2016. Neither authors nor journals were blinded to reviewers. No language restriction was set; studies in languages other than English or German were translated by native speakers.

2.4. Search strategy

The following search was adapted for each database:

((((((((((((((((mottled enamel) OR non endemic mottling of enamel) OR internal enamel hypoplasia) OR cheese molars) OR non-fluoride enamel opacities) OR idiopathic enamel opacities) OR enamel hypomineralization) OR enamel hypomineralisation) OR hypomineralized molars) OR hypomineralized molars) OR molar incisor hypomineralization) OR molar incisor hypomineralisation) OR molar-incisor hypomineralization) OR molar-incisor hypomineralisation) OR molar-incisor-hypomineralization) OR molar-incisor-hypomineralisation) OR mih)) AND ((((((management) OR treatment) OR orthodontics) OR extraction) OR first permanent molar) OR clinical).

2.5. Selection process

Both authors (FS, KE) independently screened titles and then compared their findings. In the case of disagreement, titles were included to obtain full texts. Full texts were assessed independently after de-duplication. Studies were included after agreement with a consensus in cases of disagreement being reached through discussion.

2.6. Data collection process

A pilot-tested spreadsheet was used for data extraction, which was performed independently by both reviewers (FS, KE). No disagreements occurred.

2.7. Data items

The following items were collected: Author names, year of publication, sample size, sample characteristics, type of intervention, drop-out rate, results and risk of bias.

2.8. Outcomes

The study findings for our primary and secondary outcomes and outcome measures were extracted. For studies reporting non-significant findings without any further information, this was extracted to potentially allow sensitivity meta-analysis (which was eventually not possible).

2.9. Quantitative synthesis

The synthesis was performed for annual failure rates in restorative trials. For other groups of treatments, pooling of data was not possible or needed as only one intervention was investigated. The unit of analysis was the tooth; clustering is thus possible and standard deviations of pooled failure rates are likely wider than estimated. As we did not aim to statistically compare rates (given the low number of studies supporting each intervention), this was accepted. Annual failure rates were sample size weighted for pooling.

2.10. Risk of bias

For controlled trials, Cochrane's risk of bias tool [21] was originally planned to be used. As most studies were observational in character, the Newcastle-Ottawa scale (NOS) was instead used for risk of bias assessment of all trials [22], evaluating selection and comparability of cohorts, assessment of outcomes and exposure ascertainment. NOS scores of 0–5 were assumed to indicate a high risk of bias, while 6–7 indicated moderate and 8 low risks of bias.

3. Results

3.1. Study selection

From 2420 identified studies, 64 were evaluated full text, and 14 clinical trials included (Fig. 1,Tables 1 and 2). Excluded studies and reasons for exclusion can be found in the appendix (Table S1).

From the included studies, 10 discussed different treatment modalities for MIH-affected molars (four prospective and four retrospective cohort studies, two randomized trials). In total, 381 participants (720 molars) were treated. The mean follow-up was 3.6 (1.0–8.3) years (Table 1).

Four studies discussed different treatment modalities for MIH-affected incisors (two prospective cohort studies and two randomized trials). A total of 139 participants had been treated, with overall 274 incisors. The mean follow-up was 0.5 (0.1–2.5) years (Table 2).

3.2. Findings for molars

One trial investigated remineralization treatment on 30 molars, following them over 3 years, and found improvement in the morphology of the molar surface (Tables 1 and 3). Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) was shown to have a remineralizing and a desensitizing effect on MIH teeth by creating a stable super saturated solution of calcium and phosphate at the enamel surface [23–25]. There were no significant differences of the desensitizing effect between CPP-ACP with or without added fluoride [25].

Restorative approaches had been taken in a number of trials (Table 3). Two studies on a total of 129 molars investigated fissure

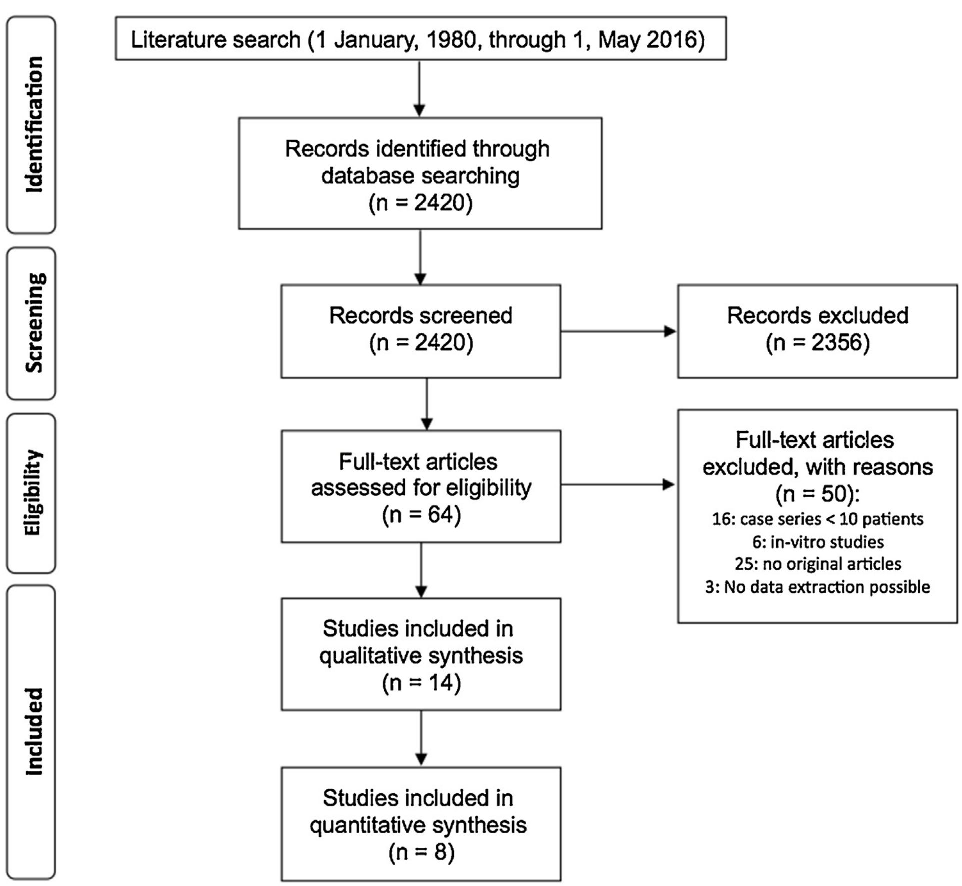

Fig. 1. Flow-chart of the study.

Table 1
Included studies on treatments in molars (studies ordered chronologically).

Author/s	Type	N	Age (y)	Gen	Nt	Severity	Intervention	Follow-up (m)	Results
Koch and Garcia-Godoy [2000] [54]	Pro Co	12	6–8	n/a	41	n/a	4 composite crowns 8 ceramic crowns 29 gold crowns	24–60	41/41 (100%) success
Lygidakis et al. [2003] [26]	Pro Co	46	8–10	n/a	49	Severe	Composite (18 two surfaces, 31 three surfaces)	48	49/49 (100%) success
Zagdwon et al. [2003] [28]	RCT	17	6–16	6 M, 11 F	42	Severe	(A) 19 PMC (B) 23 adhesive casts	12–24	(A) 18/19 (94.7%) success (B) 21/23 (91.3%) success Adhesive casts 4 times more expensive than PMCs
Kotsanos et al. [2005] [32]	Retro Co	72	8	38 M, 34 F	136	n/a	(A) 35 sealants (B) 18 amalgam (C) 59 composite (D) 24 PMC	52	(A) 87.1% success (B) 38.9% success (C) 74.6% success (D) 100% success
Mejare et al. [2005] [27]	Retro Co	76	6–17	31 M, 45 F	153	Mild and severe	(A) 63 GIC (B) 14 compomer (C) 34 composite (D) 32 amalgam (E) 1 PMC (F) 9 castings	62	(A) 49.2% success (B) 64.3% success (C) 85.3% success (D) 78.1% success (D) 100% success (F) 100% success 5/153 with pulp necrosis (unclear in which groups)
Jälevik and Möller [2007] [29]	Retro Co	27	6–13	15 M, 18 F	70	Severe	Extraction with or without orthodontics	44–99	Maxilla: 22/40 tooth (55%) space closure without intervention (success) Mandible: 14/30 tooth (47%) space closure without intervention (success)
Lygidakis et al. [2009] [42]	RCT	47	6–7	n/a	94	Mild	(A) Adhesive + FS (B) Conventional FS	48	(A) 33/47 (70.3%) success; 14/47 (29.7%) partially sealed (failure) (B) 12/47 (25.5%) success; 21/47 (44.6%) partially sealed (failure); 14/47 (29.7%) complete loss (failure)
Baroni and Marchionni [2011] [23]	Pro Co	30	6–9	n/a	30	n/a	CPP-ACP	36	Improvement in the enamel morphology
Gaardmand et al. [2013] [55]	Retro Co	33	8–18	17 M, 16 F	57	Severe	Cast adhesive gold copings	Mean 38.6	56/57 (98.2%) success
Fragelli et al. [2015] [56]	Pro Co	21	6–9	12 M, 9 F	48	Severe	GIC	12	15/21 (78%) success

Abbreviations: CPP-ACP: casein phospohopeptide-amorphous calcium phosphate; N, number of participants; Nt, number of teeth; Gen, gender; n/a, not available; m, months; Pro Co, prospective cohort; Retro Co, retrospective cohort; RCT, randomized controlled trial; M, male; F, female; PMC, preformed metal crown; GIC, glass ionomer cement; FS, fissure sealant.

Table 2
Included studies on treatment in incisors (studies ordered chronologically).

Author/s	Study design	N	Age (Y)	Gen	Nt	Intervention	Follow-up (m)	Results
Welbury [1991] [57]	Pro Co	66	6–18	n/a	52	Composite resin veneers	6–30	45/52 (86%) success
Wong and Winter [2002] [45]	Pro Co	15	n/a	n/a	30	Microabrasion	6	10/15 (66.6%) of the patients were satisfied (success) with their appearance after micro-abrasion
Özgül et al. [2013] [25]	RCT	33	7–12	n/a	92	Fluoride, Ozone + Fluoride, CPP-ACP Ozone + CPP-ACP, CPP-ACP + Fluoride, all combined	1	Desensitizing agents reduced hypersensitivity. CPP-ACP more effective, ozone prolonged the effect of CPP-ACP.
Sheoran et al. [2014] [58]	RCT	25	11–13	n/a	100	(A) Microabrasion with 37% phosphoric acid and pumice paste (B) Microabrasion with 18% HCl and pumice paste	1	(A) 49/50 (97.2%) reduction in opacities (success) (B) 48/50 (96.7%) reduction in opacities (success)

Abbreviations: N, number of participants; Nt, number of teeth; Gen, gender; n/a, not available; m, month; Pro Co, prospective cohort; RCT, randomized control trial; M, male; F, female; HCl, hydrochloric acid; CPP-ACP, casein phosphopeptide-amorphous calcium phosphate.

sealants, following them over a mean of 4 years. Three studies on a total of 132 molars assessed composite restorations, following them over a mean of 4.5 years. Two studies on a total of 107 molars assessed glass ionomer cement (GIC) restorations, following them over a mean of 3 years. Two studies on a total of 50 molars assessed amalgam restorations, following them over a mean of 5 years. One study on a total of 14 molars assessed compomer restorations, following them over 5.2 years. Two studies (43 molars) followed performed metal crowns (PMCs) over a mean period of 3.1 years, another study assed only one PMC and therefore was not included in the performed synthesis (see below). Indirect metal, composite or ceramic restorations had been assessed by four studies (130 molars), with a mean follow-up of 5 years. Estimated mean [SD] annual failure rates were highest for fissure sealants (12 [6]%) and glass ionomer restorations (12 [2]%), and lowest for indirect restorations (1[3]%), PMCs (1.3 [2.1]%) and composite restorations (4[3]%) (Fig. 2). The annual failure rates should be interpreted carefully, as the severity of MIH was not reported for all studies, but

Table 3
Assessed treatments. For detailed risk of bias assessment, see Table S2.

Study	Severity	Sample size	Intervention	Follow-up (m)	Drop-out	Results	Risk of bias
Remineralization							
Baroni and Marchionni [2011] [23]	n/a	30 molars	Casein phospopeptide-amorphous calcium phosphate (CPP-ACP)	36	0	Improvement in the enamel morphology after the use of CPP-ACP	High
Özgül et al. [2013] [25]	n/a	92 incisors	Fluoride, Ozone + Fluoride, CPP-ACP Ozone + CPP-ACP, CPP-ACP + Fluoride, all combined	1	0	Desensitizing agents reduced hypersensitivity. CPP-ACP more effective, ozone prolonged the effect of CPP-ACP.	Low
Fissure sealants (FS)							
Kotsanos et al. [2005] [32]	n/a	35 molars	FS	54	0	22/35 (87.1%) success	Moderate
Lygidakis et al. [2009] [42]	Mild	94 molars	Adhesive + FS Conventional FS	48	0	33/47 (70.3%) success; 14/47 (29.7%) partially sealed (failure) 12/47 (25.5%) success; 21/47 (44.6%) partially sealed (failure); 14/47 (29.7%) complete loss (failure)	Low
Composite restorations							
Lygidakis et al. [2003] [26]	Severe	49 molars	Composite	48	0	49/49 (100%) success	Moderate
Kotsanos et al. [2005] [32]	n/a	59 molars	Composite	54	0	44/59 (74.6%) success	Moderate
Mejare et al. [2005] [27]	Mild and severe	34 molars	Composite	62	0	29/34 (85.3%) success	Moderate
Glass ionomer cement (GIC) restorations							
Mejare et al. [2005] [27]	Mild and severe	63 molars	GIC	62	0	31/63 (49.2%) success	Moderate
Fragelli et al [2015] [56]	Severe	48 molars	GIC	12	4	38/44 (78%) success	High
Compomer restorations							
Mejare et al. [2005] [27]	Mild and severe	14 molars	Compomer	62	0	9/14 (64.3%) success	Moderate
Amalgam restorations							
Kotsanos et al. [2005] [32]	n/a	18 molars	Amalgam	54	0	7/18 (38.9%) success	Moderate
Mejare et al. [2005] [27]	Mild and severe	32 molars	Amalgam	62	0	25/32 (78.1%) success	Moderate
Preformed metal crowns (PMC)							
Zagdwon et al. [2003] [28]	Severe	19 molars	19 PMCs	12–24	0	18/19 (94.7%) success	Low
Kotsanos et al. [2005] [32]	n/a	24 molars	24 PMCs	50	0	24/24 (100%) success	Moderate
Indirect cast restorations (ICR)							
Koch and Garcia-Godoy [2000] [54]	n/a	41 molars	4 composite 8 ceramic 29 gold	36	0	4/4 (100%) success 8/8 (100%) success 29/29 (100%) success	High
Zagdwon et al. [2003] [28]	Severe	23 molars	Nickel chrome alloy	12-24	0	20/23 (91.3%) success	Low
Mejare et al. [2005] [27]	Mild and severe	57 molars	Gold and porcelain	62	0	9/9 (100%) success	Moderate
Gaardmand et al. [2013] [55]	Severe	9 molars	Gold copings	38.6	4	56/57 (98.2%) success	Moderate
Extraction							
Jälevik and Möller [2007] [29]	Severe	70 molars	Extraction	44–99	3 (7 teeth)	Maxillary: 22/40 tooth (55%) space closure without intervention (success) Mandibular: 14/30 tooth (47%) space closure without intervention (success)	Moderate
Microabrasion							
Wong and Winter [2002] [45]	n/a	30 incisors	Microabrasion with abrasive paste +18% HCl	6	0	10/15 (66.6%) of the patients were satisfied (success)	High
Sheoran et al. [2014] [58]	n/a	50 pairs of incisors	37% phosphoric acid and pumice paste 18% HCl and pumice paste	1	0	49/50 (97.2%) reduction in opacities (success) 48/50 (96.7%) reduction in opacities (success)	Low
Composite resin veneers							
Welbury [1991]	n/a	52 anterior teeth	Composite resin veneers	6–30	0	45/52 (86%) success	Moderate

Abbreviations: n/a, not available; m, months; PMC, preformed metal crown; GIC, glass ionomer cement; FS, fissure sealant; HCl, hydrochloric acid; CPP-ACP, Casein phosphopeptide-amorphous calcium phosphate.

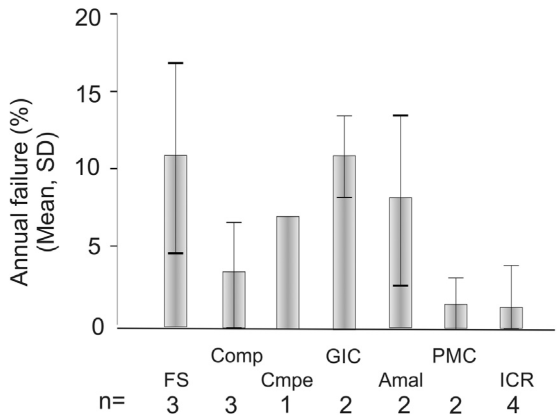

Fig. 2. Mean (SD) annual failure rates of different restorative treatments: Fissure sealants (FS), composite (Comp), compomer (Cmpe), glass ionomer cement (GIC), amalgam (Amal) restorations, preformed metal crowns (PMCs) and indirect cast restorations (ICR). n: number of studies included for synthesis. If n = 1, error bars are missing.

could be heavily confounding risk of failure. Only two studies recorded on pulpal complications [26,27]. One study additionally reported on the cost-effectiveness of indirect versus preformed metal crowns, and found indirect restorations significantly more expensive due to laboratory costs being incurred [28].

One retrospective cohort study had evaluated extraction of MIH affected first permanent molars and subsequent spontaneous alignment of the second molars [29]. Overall 27 children aged 5.6–12.7 (median 8.2) years at the extraction were evaluated. A median of 2.6 molars were extracted in each participant (overall number was 70 extracted molars). Seven participants (26%) had common malocclusions like crowding or crossbites. 79% of the extractions took place in a quadrant where a third molar was present; in three participants, all third molars were missing, while in two participants, two third molars were missing. The eruption of the second molars followed after a mean period of 6 years after extraction. In the maxilla 55% and in the mandible 47% of second molars aligned spontaneously and did not require an orthodontic intervention. The authors of the study did not report on influencing factors for alignment (like stage of second molar development or vertical skeletal dimension).

No study reported on the subjective impact of treatments on patients. Adverse events (allergy to restorative materials etc.) were not reported.

3.3. Findings for incisors

For incisors, three different strategies were investigated; one for controlling hypersensitivity and two for improving aesthetics of MIH incisors (Tables 2 and 3).

For controlling hypersensitivity, desensitizing agents were applied in one study on 92 incisors. These were followed over only one month, with improvement found in all incisors.

For aesthetics, two studies with 40 participants investigated micro-abrasion. Teeth were followed over 0.3 (0.1–0.5) years. The mean success rate (i.e. the proportion of teeth with aesthetical improvement) was 81%. One study used composite veneers instead, treating overall 52 teeth. These were followed over 1.5 (0.5–2.5) years, with a similar success rate (86%).

Further data on secondary outcomes like costs or adverse events were not reported.

3.4. Risk of bias

Of the 14 studies, 4 showed high, 6 showed moderate and 4 showed a low risk of bias (Table S2). Most studies suffered from limited comparability between groups and did not sufficiently control for possible confounders (severity of MIH, the age of patients). Moreover, a clear outcome definition, reporting or unbiased ascertainment was missing in many studies. The small sample size, oftentimes distributed over different treatment types, and selection as well as detection bias led to uncertainty and high risk of bias of most studies.

4. Discussion

Molar-incisor hypomineralization is associated with significantly increased dental treatment needs, especially in severe cases [27,30–34], as porous enamel and possible post-eruptive breakdown promote bacteria dentin penetration, which leads to pulpal inflammation and hypersensitivity or pain [1,3,35,36]. The resulting chronic pulpal complicates local anesthesia [37] as a consequence, children with MIH are more likely to have dental anxiety and fear [31]. The specific hard tissue conditions in MIH, the hypersensitivity of MIH teeth and the anxiety of affected children are challenging dental practitioners. The present reviewed reported on various treatment strategies for MIH and evaluated them quantitatively and qualitatively.

The included studies were mainly observational and prone to risk of bias. Most studies did not randomly allocate treatments to teeth, with the inherent risk of indication bias (teeth with more severe MIH or hypersensitivity might have received different interventions than mild cases). That is why we only present pooled annual failure rates but omitted more sophisticated statistical pooling or comparison of risk of failure. Moreover, the yielded samples were usually recruited from specialized centers and might not be representative for the population of children with MIH found in general practices. A number of interventions were similarly “uncommon” in general practice and have limited applicability in primary care. As a consequence, the external validity of included studies is limited. As treatments were not allocated at random, possible bias by confounding (severity of MIH, hypersensitivity status, the age of the patient, affected number of surfaces) needs to be accounted for. This was not the case, and most studies did not report sufficiently on these confounders. Again, this should be borne in mind when comparing annual failure rates of treatments. Outcome ascertainment was usually prone to detection bias, as examiners were not blinded. One should, however, note that blinding is only limitedly possible or fully impossible in many cases, as different treatments (like gold versus ceramic restorations) cannot be blinded. The same applies for blinding of operators and patients. The chosen outcomes are mainly restorative ones, with limited relevance to patients (who might be more interested in the alleviation of pain, or aesthetics). This calls for the definition of a core outcome set for MIH studies. In line with this, a minimum follow-up should be defined, as many relevant aspects (like long-term complications and need for re-interventions, for example after extraction) cannot be assessed short-term. Moreover, sample sizes were usually small, resulting in a lack of power for any syntheses and great uncertainty. Multi-center (practice-based) studies might be needed to yield sufficient samples and also to overcome the limited generalizability of findings.

We found different treatment options to have different suitability. The majority of studies investigated restorative approaches towards MIH. It can be noted that amalgam restorations showed high failure rates in MIH molars. Amalgam is a non-adhesive material and its use in atypically shaped MIH-cavities does not seem indicated. Moreover, the lack of bonding and the need for retentive cavities might aggravate existing substance defects via preparation and further enamel breakdown adjacent to the material [38–40]. Adhesive restorations or sealants seem more suitable, but the enamel-adhesive interface in MIH is more porous, leading to enamel cracks and decreased bond strength compared with sound enamel. As a result, cohesive failure is oftentimes noted in restorations bonded to MIH-enamel [41]. As fissure sealants are solely retained via such adhesion, it seems logic that annual failure rates are relatively high, as confirmed by this review. Using an acetone-containing adhesive system prior to sealing seems to increase retention rates and could be recommended [26,42]. Regular resealing might also be accepted in case this avoids invasive therapies.

When MIH defects of carious lesions in MIH enamel need direct restorations, composite seems the most suitable material, as it is bonded to the enamel without the need of retentive preparations. There is some indication that compared with etch-and-rinse adhesives, self-etch materials could yield similar or even superior bonding results to MIH enamel, something to consider given the easier application and the omission of etching and rinsing, which could both cause pain during treatment [41]. Based on our findings, GIC may be used for temporization of teeth, e.g. in cases of difficult moisture control during eruption, and might provide some benefit via fluoride release. The long-term retention of these restorations seems limited, probably as they have a low wear and fracture resistance [40], the latter being especially relevant in cavities involving cusps or margin ridges, as is frequently the case with MIH.

As an alternative to temporary direct restorations, PMCs might be used. Two studies evaluated this treatment and showed high success rates. Moreover, the ease of application and the potentially beneficial cost-effectiveness of this treatment seem advantageous when comparing PMCs with indirect restorations [27,28,32]. The latter, in our case composite, ceramic, or cast restorations, showed high success rates. However, only a few patients were treated with each indirect restoration type and followed over limited time frames. Future studies should assess the applicability of indirect restorations in MIH and the subjective impact of this treatment on patients. Moreover, future studies should aim for developing a treatment pathway in MIH patients, with possible non-restorative treatments or direct restorations or PMCs being placed in children or adolescents, and indirect restorations being used in adults in case of repeated failure of less invasive therapies.

In severe MIH, tooth removal might be an option, as the spiral of escalating re-interventions and the associated burden of dental procedures could be avoided. Based on the present review, the subsequent spontaneous space closure occurs more often in the maxilla than the mandible. This is in line with findings from a recent systematic review by Eichenberger et al. [43] built on six clinical studies. However, it is worth highlighting that the treated patients were relatively young, and usually had a third molar in development. It is unlikely that such alignment occurs similarly well if extractions were performed in older patients. Further factors like the presence of a general malocclusion, the exact timing of extraction, and the status of neighboring teeth were not fully reported, but need be taken into consideration when making the grave treatment decision for extraction. Similarly, the specific conditions of the 2nd and 3rd molar should be evaluated prior extraction. If no alignment occurs, orthodontic therapy might often be required, again generating costs and burdening the patients. Last, it should be highlighted that only one study [29] assessed spontaneous space closure after extracting MIH molars (one other study also evaluated extraction, but reported insufficient data for inclusion in this review) [27].

For mild cases as well as for aesthetic purposes (mainly in incisors), remineralization therapies might be an option. The aesthetic appearance due to MIH was shown to impact on the child's quality of life and socio-psychological status [3,34]. Given the age of these patients, restorative interventions like veneers should be avoided or postponed, and less invasive strategies preferred. Besides remineralization (only casein phosphopeptide-amorphous calcium phosphate had been tested clinically for this purpose) [23,24], micro-abrasion could be an option, while the associated substance loss was shown to be significant in severe cases [44–48]. A combination of etching, bleaching and sealing MIH incisors and affected areas might be an alternative [49,50]. Similarly, resin infiltration has been tested in vitro, showing unreliable infiltrating effects. Prior to infiltration, a specific protocol for removal of proteins from enamel pores might be needed; this has so far not been established [51].

4.1. Recommendations for future research

A number of recommendations can be deduced from this review. Future studies should aim to include a relevant number of patients and follow them for sufficiently long periods to allow meaningful conclusions. Confounding factors like patient's age, hypersensitivity, MIH severity, and lesion appearance should be recorded. For the latter, a color coding seems useful, as yellow or yellow-brownish defects are oftentimes deeper and more porous than creamy-yellow or whitish defects [52], with different risks of breakdown and hypersensitivity, and different substrate for adhesive treatments. For outcomes, not only clinical but also subjective and cost-effectiveness parameters should be collected. Reporting should adverse events like the allergy to specific materials. Controlled trial designs should be used if possible, and blinding attempted (e.g. in remineralization trials).

4.2. Recommendations for clinicians

Early diagnosis of MIH is essential to allow provision of preventive or early restorative intervention for MIH teeth to avoid the induction of pulpal inflammation and pain, which in turn complicate any further treatments. Such early detection can be complemented by risk before or during eruption of permanent teeth, building on a detailed medical history on possible causative factors (like the use of drugs during pregnancy, birth complications, or medical issues in the first 3–4 years of the child's life), as well as assessment of primary teeth for deciduous molar hypomineralization (DMH) [53]. If MIH is detected, both the patient and the parents need to be informed about the consequences of MIH and the associated risks of hypersensitivity and caries incidence. A short recall period should be established alongside any required therapeutic measures. Both this recall period and therapeutic measures should be chosen considering the assumed severity of MIH according to the discussed color scale as well as the presence of symptoms.

First and foremost, hypersensitivity needs to be addressed; as such hypersensitivity impairs tooth brushing and thus increases the risk of caries for MIH teeth (mainly molars). Remineralization using CPP-APC (and most likely also fluoride, while insufficient data is available to support fluoride application for MIH) seems suitable to reduce mild or moderate hypersensitivity in MIH teeth. Alternative, fissure sealants could have some benefits for mild MIH in molars, as they further assist the prevention of caries and enamel breakdown.

For more severe defects in molars, composite restorations, PMCs or indirect restorations could be used, while the specific timing of when to best place different restoration types are unclear at present. Only for severe MIH, extraction should be performed, and the option and need for subsequent orthodontic therapy should be considered prior treatment commencement. In incisors, aesthetics will oftentimes be the most important aspect. A long-term treatment concept starting with remineralization therapy, over infiltration and micro-abrasion to composites, veneers and crowns should be considered.

In conclusion, a limited number of mainly observational studies investigated treatment options for MIH. For molars, non-invasive and invasive/restorative options are available; the indication for which should be based on the severity of MIH and hypersensitivity. If restorations are needed, composites, preformed metal crowns or indirect restorations seem suitable. Prior to tooth extraction as last resort factors like the presence of a general malocclusion, patients' age and the status of neighboring teeth should be considered. No clear recommendations can be given for MIH incisors. Future studies should aim for high internal and external validity, follow-up patients for longer time periods and use outcomes relevant to patients, providers, and public services.

Conflict of interest

There is no conflict of interests to be reported.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdent.2016.09.012.

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