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Review Article | **Dentistry**

Rebuilding the Strength of Hypomineralized Enamel – An In-Depth Systematic Literature Review

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Abstract

Molar Incisor Hypomineralization (MIH) is a prevalent developmental enamel defect characterized by qualitative changes in the enamel of one or more first permanent molars, often accompanied by similar defects in the incisors. This condition leads to significant dental challenges, including soft, porous enamel, which is more susceptible to damage and caries than non-MIH teeth. The affected teeth exhibit lower mineral concentration, higher porosity, and altered mechanical properties, contributing to their increased vulnerability to decay and restoration failures. Research indicates that MIH-affected teeth often require more extensive dental treatments due to compromised structural integrity. The enamel defects associated with MIH manifest as well-demarcated opacities, which can lead to hypersensitivity and aesthetic concerns for patients, particularly children. However, there is hope in the form of various remineralization strategies that have been explored to address MIH's challenges. These strategies, including recent clinical trials, have demonstrated the efficacy of remineralization agents in restoring some of the lost enamel properties, which is crucial for managing MIH effectively. This potential for restoration through remineralization strategies offers a hopeful outlook for improving patient outcomes with MIH.

Keywords: Molar Incisor Hypomineralization, hypomineralized enamel, remineralization, Fluoride, developmental defects.

INTRODUCTION

Molar incisor hypomineralization (MIH) is a condition that affects a significant portion of the population, with a prevalence of 4-25% [1, 2]. It is characterized by enamel hypomineralization, primarily affecting one or more first permanent molars (FPMs) and often associated with affected incisors [3]. This condition is caused by disrupted ameloblastic function during the transitional and maturational stages of enamel development, resulting in deficient enamel minerals [3]. The affected teeth have soft and porous enamel, leading to white, yellow, or brown discoloration. The porous enamel may fragment soon after the eruption, resembling hypoplasia. The smooth and fragile enamel can ultimately break down under the masticatory forces, resulting in partial or complete loss of crown structure, known as post-eruptive breakdown (PEB) [3, 4]. Due to the porous nature of the enamel, these teeth are susceptible to damage from various stimuli, including brushing, presenting significant challenges in Pediatric Dentistry and Restorative Dentistry [5]. The impact of MIH on dental health is substantial, necessitating immediate attention and improved treatment strategies to prevent further deterioration.

Restoring MIH-affected molars is a complex task, presenting substantial challenges. Issues such as repeated marginal breakdown, frequent restoration loss, and disruption of the cavity surface, leading to secondary caries and frequent restoration replacement, are common. Statistics have shown that MIH-affected molars undergo dental treatment nearly nine times more often than non-MIH molars, and every defective tooth, on average, is treated twice [6]. These findings underscore the substantial challenges in restoring MIH-affected molars. It is crucial to develop and implement improved treatment strategies and materials to prevent further deterioration of MIH-affected teeth, highlighting the complexity and urgency of the situation. To explore the challenges and treatment strategies for Molar Incisor Hypomineralization (MIH), a prevalent enamel defect affecting first permanent molars and incisors, by investigating the qualitative changes in enamel properties and assessing the efficacy of various remineralization techniques aimed at improving patient outcomes.

Planning and performing the review/Search strategy

The initial step in conducting the review involved clearly defining its objective: to examine all relevant articles and case studies focused on rebuilding the strength in hypomineralized enamel. To develop an effective search strategy, a pilot search was first performed to refine the search terms and identify relevant databases. Comprehensive searches were conducted across PubMed and Google Scholar, covering their entire duration from inception until July 2024. Only articles published in English were considered, without any limitations on the year of publication. The prior literature's most frequently cited descriptors, combining Medical Subject Headings (MeSH) and text words to ensure thoroughness. Broad inclusion criteria were applied to capture a wide range of studies, facilitating an exhaustive systematic review of the available evidence on the subject. The mesh terms and entry terms used were “MIH OR molar incisor hypomineralization OR molar incisor hypomineralisation AND toothpaste OR dentifrice AND remineralization OR remineralizing agents OR CPP-ACP OR GC tooth mousse OR MI paste OR calcium sucrose phosphate OR Tooth mousse OR Recaldent AND Fluoride varnish.”

Understanding the unique characteristics of MIH in teeth

Teeth affected by MIH exhibit unique characteristics that significantly alter their mechanical properties and susceptibility to caries. These include lower mineral concentration, less organized crystalline structure, greater porosity (15-21 times more), higher carbonate content, and a lower Ca/P ratio (reduced by almost 5-20%) [7]. These factors result in altered mechanical properties, reduced hardness, and modulus of elasticity of hypomineralized enamel compared to normal enamel. Furthermore, the increased carbonate content in hypo-mineralized enamel significantly increases its susceptibility to caries [7, 8]. The carbonated hydroxyapatite crystals in this type of enamel are less resistant to dissolution when subjected to acid attack, posing a severe threat to dental health [9]. The observed hypomineralized changes in teeth affected by MIH reflect changes occurring on an ultra-structural level and are associated with changes in the refractive index of the affected enamel [10]. Severe cases of this condition show maximum disruption, resulting in unorganized and degraded enamel [1, 3]. The increased porosities in MIH-affected enamel further highlight the unique characteristics of MIH-affected teeth and the complexity of the condition.

The condition is often associated with various genetic and environmental factors, influencing its prevalence and severity [11]. Understanding these factors can aid in the development of targeted preventive strategies. For instance, children with a history of hypomineralized second primary molars are at a higher risk for developing MIH, indicating the need for early intervention and monitoring [12]. Furthermore, identifying MIH during routine dental examinations is crucial, as early detection can facilitate timely preventive measures and treatment [13].

Role of remineralization in early white spot lesions

Hydroxyapatite is the main inorganic component of dentin and enamel. The ability of saliva to remineralize teeth is well-documented [14]. Saliva delivers calcium and phosphate ions in a readily available form for developing and maintaining hard tissues throughout life [15]. Saliva is saturated with phosphoprotein-stabilized calcium and phosphate ions at normal pH levels, ensuring they can penetrate mineral-deficient lesions [15, 16]. However, longitudinal studies have found that most white spot lesions (WSL) remain largely unaffected after two years, with only some getting smaller [17, 18]. Furthermore, natural salivary remineralization is a slow process, and mineral gain tends to occur only on the surface of the WSL due to the low ion concentration gradient from saliva into the lesion [19]. Fluoride-mediated salivary remineralization is also limited to the outer 30 μm of the tooth, and it does not improve the subsurface lesion's appearance or structural properties [20, 16]. It is suggested that additional external sources of stabilized calcium and phosphate ions could enhance the natural remineralization potential of saliva by promoting faster and deeper subsurface remineralization through increased diffusion gradients.

The rationale for the use of remineralizing agents in MIH

The mineral content of the enamel and its mechanical properties are directly correlated, and hypomineralized enamel has a lower mineral content and inferior mechanical properties [21]. Hence, an increase in the mineral density of the enamel can improve its properties, subsequently improving its resistance to breakdown and caries development. Remineralizing agents have been found to increase the mineral density of hypomineralized enamel in MIH-affected teeth [22-25]. The routine use of topical remineralization agents, such as fluorides, has been recommended. However, the evidence for different treatment protocols for this patient group is low. The rationale for remineralization techniques is to increase the mineral content of the hypomineralized dental tissues to improve their physical properties and subsequently enhance their resistance to breakdown and caries development [26]. Therefore, there is a need for new agents and more research for the oral care of MIH patients.

Use of the concept of remineralization in hypomineralized enamel

In young teeth, enamel functions as a permeable membrane for small ions, such as calcium and phosphate, as demonstrated by Bertacci *et al*., 2007 [27]. This property supports the rationale for supplementing these ions to enhance dental health. Furthermore, enamel acts as a semi-permeable membrane for larger molecules, which justifies using casein peptides as a supplement. Baroni and Marchionni 2011 indicate that combining calcium and phosphate ions with larger molecules could be beneficial in treating MIH teeth, characterized by deficiencies in these essential minerals [28]. While clinical success has been achieved over many years, the scientific evidence supporting the effectiveness of fluoride and other remineralizing agents in treating MIH is still evolving.

The literature describes several techniques for remineralizing MIH lesions. These techniques include applying toothpaste and varnishes containing fluoride (with or without tricalcium phosphate), casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), or casein phosphopeptide-amorphous calcium fluoride phosphate (CPP-ACFP).

Fluoride enhances the remineralization process, which is vital for teeth exhibiting hypomineralization. Regular fluoride treatments can help stabilize the enamel and prevent further deterioration, making it an essential component of preventive care for children with MIH.

Fluoridated toothpaste is also a fundamental aspect of preventive care for MIH. The recommendation for children to use fluoridated toothpaste twice daily is supported by evidence indicating that fluoride can significantly reduce caries risk and promote enamel remineralization [29]. Incorporating fluoride into the daily oral hygiene routine is particularly beneficial for children with MIH, as it helps strengthen the enamel and mitigate the effects of hypomineralization [30]. Fluoride toothpaste has been associated with reducing dental caries, particularly in children with MIH, as it helps reinforce the enamel and promote remineralization [31]. Furthermore, incorporating additional remineralizing agents in toothpaste formulations, such as CPP-ACP, can enhance the protective effects against caries in MIH-affected teeth [32].

Hydroxyapatite (HAP) toothpaste is as effective as fluoride in remineralizing initial caries lesions and preventing dental decay. It also offers the added benefit of eliminating the risk of fluorosis and other side effects associated with fluoride. The HAP particles synthesized for these toothpastes are structurally like the crystallites in human enamel, allowing them to penetrate the enamel surface and mimic its properties readily. It can serve as a calcium and phosphate ions source and an acid buffer in bacterial biofilms. A notable randomized clinical trial in Germany tested a fluoride-free HAP toothpaste for managing MIH and reported a reduced MIH-associated hypersensitivity in children [33]. Compared to the fluoride control group, children using the HAP toothpaste tended to experience less hypersensitivity related to MIH. HAP exhibits high biocompatibility and can be easily incorporated into daily oral hygiene routines through toothpaste and mouthwashes. In a 2022 study, Amaechi B. T *et al*., found that toothpaste with microcrystalline hydroxyapatite is more effective in remineralizing enamel lesions than fluoride toothpaste. The study also suggested that pre-treating the tooth surface with an acid etchant enhances remineralization [34].

Topical fluoride varnish application is another critical preventive strategy for managing MIH. Fluoride varnish, particularly when applied biannually, has been shown to enhance the remineralization of hypomineralized enamel and reduce the incidence of caries in MIH-affected teeth [29, 42]. Fluoride promotes the deposition of minerals in the enamel, strengthening the tooth structure and making it more resistant to acid attacks from dietary sources.

The application of fluoride varnish, especially in conjunction with other remineralizing agents such as Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP), has demonstrated significant efficacy in improving the condition of MIH-affected teeth [35]. The combination of fluoride and CPP-ACP not only aids in remineralization but also helps desensitize the affected teeth, a common concern among patients with MIH [32] Clinical trials have demonstrated that fluoride varnish can significantly enhance the mechanical properties of MIH-affected teeth, improving aesthetic appearance and sensitivity [37, 38]. However, while fluoride varnish is effective, some studies indicate that its remineralization potential may not be as pronounced as combined treatments involving CPP-ACP [39, 40].

On the other hand, CPP-ACP has been shown to create a supersaturated environment of calcium and phosphate ions, which is essential for enamel remineralization [29]. Applying CPP-ACP can increase the mineral content of MIH-affected enamel, thereby improving its structural integrity and reducing sensitivity [35, 41]. Furthermore, combining CPP-ACP with fluoride has been suggested to yield synergistic effects, enhancing the overall remineralization process [22, 43]. Studies have indicated that using CPP-ACP with fluoride varnish results in greater remineralization efficacy than fluoride alone [44, 45].

Self-assembling peptides (SAP), particularly the peptide P11-4, have emerged as a promising approach for remineralizing enamel lesions, including those associated with MIH. These peptides are designed to mimic natural enamel proteins and facilitate the formation of a biomimetic matrix that can enhance the remineralization process. The unique properties of P11-4 allow it to penetrate demineralized enamel, promoting hydroxyapatite crystallization and effectively reversing early carious lesions. Research indicates that SAP can significantly outperform traditional fluoride treatments in terms of remineralization efficacy. For instance, Gohar et al., 2022 demonstrated that P11-4 resulted in more significant lesion regression than fluoride varnish in post-orthodontic white spot lesions. This suggests that SAP may provide superior outcomes in enamel remineralization [46]. Similarly, Al-Baso and Al-Naimi (2022) highlighted the formation of a three-dimensional matrix that replaces degraded enamel structures, thereby facilitating subsurface remineralization [47]. This ability to create a biomimetic scaffold is crucial for effective enamel repair, particularly in cases of MIH where the enamel is structurally compromised.

Moreover, studies have shown that combining SAP with fluoride can yield synergistic effects. Applying P11-4 alongside fluoride can enhance remineralization compared to either treatment alone. This is because the peptide's monomeric form allows it to penetrate the porous structure of demineralized enamel more effectively than traditional fluoride varnishes, which primarily act on the surface [48, 49]. This deeper penetration is vital for addressing the subsurface demineralization often seen in MIH. In addition to their remineralization capabilities, SAP has been shown to induce hydroxyapatite nucleation de novo, further supporting their role in enamel repair [50]. This characteristic is particularly relevant for MIH, where the enamel's integrity is compromised, and traditional treatments may not suffice. The biomimetic nature of P11-4 allows it to interact with calcium and phosphate ions in saliva, enhancing the remineralization process and potentially reducing the risk of caries associated with MIH [51, 52]. Clinical trials have also supported the efficacy of self-assembling peptides in treating early carious lesions and reported that treatment with P11-4 led to significant remineralization of artificial carious lesions. These outperforming control groups did not receive the peptide treatment [53]. Additionally, studies have indicated that the application of P11-4 can inhibit demineralization by forming a protective layer on the enamel surface, like the natural salivary pellicle, which helps retain calcium and phosphate during the demineralization phase [54].

Notably, various studies demonstrated the efficacy of SAP in remineralizing early enamel carious lesions by augmenting the mineral content [52, 55]. Moreover, Prashant Babaji *et al*., (2019) provided evidence highlighting the superiority of SAP over CPP-ACP in the remineralization process [56].

Literature on the effectiveness of remineralizing agents on teeth affected by MIH

Molar Incisor Hypomineralization (MIH) management has garnered significant attention in dental research due to its prevalence and challenges in clinical practice. Recent studies have explored various treatment modalities to enhance enamel remineralization and reduce hypersensitivity associated with this condition.

Baroni and Marchionni's study in 2011 demonstrated that a calcium-phosphate casein product significantly improved the mineralization and morphology of hypomineralized molars over three years, supporting its remineralization efficacy [28]. This finding aligns with Kumar *et al*., 2022, who reported a notable increase in calcium and phosphorus content and a decrease in carbon content in teeth treated with fluoride varnish and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) over six months, indicating effective remineralization [57]. Similarly, Restrepo *et al*., 2016 observed significant changes in the mineral composition of hypomineralized enamel in both molars and incisors after regular fluoride varnish applications, further supporting the role of fluoride in enhancing enamel integrity. These studies collectively underscore the potential of calcium phosphate-based treatments in addressing the mineral deficits characteristic of MIH [58]. Berkant Sezer *et al*., 2018 have shown a significant change in Diagnodent pen scores from baseline to 3 months after regular application of CPP-ACPF on hypomineralized enamel of MIH-affected anterior teeth [59]. Singh *et al*., (2021) evaluated the remineralization potential of CPP-ACP-based cream and fluoride varnish for MIH-affected teeth using laser fluorescence (LF) and found that the mean change in LF values depicted a change in the mineral density scores, showing statistically significant improvement for both groups [60].

Recently, the use of LF in determining the mineral density of MIH-affected teeth has been reported with considerable success. Fridman *et al*., 2013 have shown a lower mineral density, as recorded by LF, in clinically intact enamel of MIH patients than in patients without MIH [62]. The relation between visual changes in enamel color and LF readings was also observed. However, the two groups had no significant difference regarding these changes. The study concluded that CPP-ACP cream and fluoride varnish are equally effective in remineralizing MIH-affected teeth. The Würzburg concept, developed in 2016 for German-speaking countries, introduces the MIH Treatment Need Index (MIH-TNI) and a corresponding treatment plan for practical use [36]. The updated version of the Würzburg concept now includes additional noninvasive strategies, temporary therapy options, and treatment approaches for incisors. This encompasses a wide range of treatment modalities for MIH-affected teeth, from prevention and noninvasive treatment to therapeutic approaches and, in some cases, even extraction [36]. Al-Nerabieah Z *et al*., 2024, conducted a trial that compared the effectiveness of two treatments, silver diamine fluoride (SDF) and casein phosphopeptide-amorphous calcium phosphate fluoride varnish (CPP-ACPFV), in preventing cavities and enamel breakdown in children with molar incisor hypomineralization (MIH). The study found that SDF had a lower incidence of cavities and a higher rate of stopping the progression of cavities compared to CPP-ACPFV. Both treatments were effective in preventing enamel breakdown and improving sensitivity. These findings show that SDF and CPP-ACPFV are promising treatments for controlling and managing cavities in molars affected by MIH, highlighting the importance of early intervention and appropriate dental care strategies [30]. In addition to remineralization strategies, the use of self-assembling peptides (SAP) has emerged as a promising approach for treating MIH. Singh *et al*., 2021 conducted a pilot study that showed a reduction in fluorescence scores indicative of enamel demineralization after a single application of SAP on MIH-affected incisors, suggesting its viability for enamel repair [61]. This aligns with the broader scientific consensus that integrating various remineralization techniques, including SAP and fluoride treatments, could yield enhanced outcomes for patients suffering from MIH [63].

The management of hypersensitivity in MIH-affected teeth has also been a focal point of recent research. The application of an arginine paste has been proposed to reduce hypersensitivity, demonstrating significant relief after eight weeks of treatment [64]. This was corroborated by Wang *et al*., 2016 who conducted a meta-analysis indicating that arginine toothpaste effectively decreases dental hypersensitivity [65, 66]. Furthermore, studies have shown that fluoride varnish applications also contribute to reducing sensitivity in MIH-affected teeth, reinforcing the therapeutic potential of fluoride in this context [67].

Sealants have been recommended as a preventive measure against carious lesions in MIH-affected molars. A systematic review highlighted the efficacy of giomer and resin-based fissure sealants in managing MIH, although it noted the necessity for further clinical trials to establish optimal sealing techniques and materials [5]. The application of glass ionomer sealants has also been explored, with findings suggesting they can protect against caries but may not prevent post-eruptive breakdown of MIH-affected molars [68]. The treatment of MIH involves a multifaceted approach that includes remineralization strategies, desensitizing agents, and preventive measures such as sealants. The integration of these modalities could significantly improve clinical outcomes for patients with MIH, addressing both the aesthetic and functional challenges posed by this condition.

The evaluation of remineralization strategies MIH using various remineralizing agents is a critical area of research in pediatric dentistry. Recent studies have highlighted their effectiveness in enhancing the mineral content of MIH-affected teeth. In vitro and situ studies have provided evidence supporting the efficacy of these combined treatments. For example, research has shown that applying fluoride varnish alongside CPP-ACP can significantly improve the remineralization of early carious lesions and MIH opacities [69, 70]. CPP-ACP has been associated with reducing MIH-related tooth sensitivity, further underscoring its clinical benefits [29, 71].

Despite the promising results, it is essential to note that some studies have reported methodological limitations, which may affect the generalizability of the findings [35]. Therefore, while the current evidence supports the use of both CPP-ACP and fluoride varnish for the remineralization of MIH, further well-designed clinical trials are necessary to establish definitive conclusions regarding their efficacy and optimal application protocols [72, 73].

Methods used for the assessment of remineralization in MIH

Enamel opacities and increased susceptibility to caries characterize MIH. Research on remineralization of MIH-affected teeth is crucial as it can restore enamel integrity and reduce caries risk. However, variations in methodologies used to measure remineralization effects make it difficult to compare results across studies. Several analytical techniques evaluate the remineralization of MIH-affected teeth, each with unique advantages and limitations. For instance, microcomputed tomography provides non-destructive three-dimensional reconstructions of mineral density in dental tissues [34]. Transverse Microradiography offers quantitative data on mineral content in enamel and dentin but involves invasive sample preparation, limiting its suitability for in vivo studies [22]. The Vickers microhardness test measures the hardness of enamel and dentin, indicating changes in mineral content, but is limited to surface measurements [41]. Laser fluorescence, widely used in clinical studies, detects changes in fluorescence associated with demineralization and remineralization processes [25, 59]. It is non-invasive and suitable for in vivo studies, but its sensitivity can vary. Raman microscopy offers molecular-level information about dental tissue composition, but its sophisticated equipment and expertise limit routine clinical use. Energy dispersive spectroscopy (EDS) and scanning electron microscopy (SEM) also provide valuable information but involve complex sample preparation and may not be suitable for in vivo studies [57]. The variability in methodologies poses challenges for comparing results in clinical studies, emphasizing the need for standardized analytical techniques for more reliable comparisons. Future research should prioritize adopting comparable non-invasive methods, such as laser fluorescence, to enhance result comparability and contribute to effective remineralization strategies for MIH.

CONCLUSION

The management of MIH is crucial, particularly in pediatric dentistry, as it can significantly impact oral health and quality of life. Preventive approaches are essential in mitigating the effects of MIH, and several strategies have been proposed, including sealant application in newly erupted molars, topical fluoride application, and fluoridated toothpaste.

Integrating these preventive strategies forms a comprehensive approach to managing MIH. Each method plays a vital role in protecting the enamel of affected teeth and reducing caries risk. The combination of these strategies not only addresses the immediate concerns associated with MIH but also contributes to the long-term oral health of affected children. As MIH continues to be a prevalent concern in pediatric dentistry, implementing these preventive measures is essential for safeguarding children's oral health.

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