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című program

Program- és témavezető: Dr. Varga Gábor, egyetemi tanár

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NEW FRONTIERS IN THE EARLY MANAGEMENT OF ENAMEL CARIES LESIONS AND DEFECTS

Ph.D. Thesis

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“Failures, repeated failures, are finger posts on the road to achievement. One fails forward toward success.”

– C. S. Lewis

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1. LIST OF ABBREVIATIONS

API	Approximate Plaque Index
ART	Atraumatic Restorative Treatment
BAG	Bioactive Glass
Ca	Calcium
CENTRAL	Cochrane Central Register Of Controlled Trials
CaGP	Calcium Glycerophosphate
CI	Confidence Interval
CPP-ACP	Casein Phosphopeptide–Amorphous Calcium Phosphate
CPP-ACFP	Casein Phosphopeptide–Amorphous Calcium Fluoride Phosphate
CPP-ACPFV	Casein Phosphopeptide–Amorphous Calcium Phosphate Fluoride Varnish
DH	Dentinal Hypersensitivity
DMFS	Decayed, Missing, And Filled Surfaces
DMFT	Decayed, Missing, And Filled Teeth
EAPD	European Academy Of Pediatric Dentistry
EDI	Enamel Decalcification Index
FT	Fluoride Toothpaste
FV	Fluoride Varnish

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GRADE	Grading of Recommendations Assessment, Development, And Evaluation
HVGIC	High-Viscosity Glass Ionomer Cement
ICDAS	International Caries Detection And Assessment System
LED	Light Emitting Diode
LF	Laser Fluorescence
LLLT	Low-Level Laser Therapy
MD	Mean Difference
MIH	Molar–Incisor Hypomineralization
NaF	Sodium Fluoride
PBMT	Photobiomodulation Therapy
PEB	Post-Eruptive Enamel Breakdown
PICO	Population, Intervention, Control, And Outcome
PRISMA	Preferred Reporting Items For Systematic Review and Meta-Analysis
PROSPERO	International Prospective Register Of Systematic Reviews
QLF	Quantitative Light-Induced Fluorescence
RCT	Randomized Controlled Trial
ROB	Risk Of Bias

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ROBINS-I	Risk of Bias in Non-Randomized Studies - of Interventions
RT	Randomized Trial
SCASS	Schiff Cold Air Sensitivity Scale
SD	Standard Deviation
SDF	Silver Diamine Fluoride
SMART	Silver Modified Atraumatic Restorative Technique
SMD	Standard Mean Difference
SSC	Stainless Steel Crown
TCP	Tricalcium Phosphate
USPHS	United States Public Health Service
VAS	Visual Analog Scale
WBFS/WBFPS/WBFPRS	Wong-Baker Faces Pain Rating Scale
WSL	White Spot Lesion
XMT	X-Ray Microtomography

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2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is a world where dental caries and enamel defects are detected early, and through effective non-invasive treatment and prevention, teeth are preserved, maintaining function and health. My mission is to bring evidence-based and clinically effective remineralizing agents for dental enamel caries and defects to clinical practice. In order to achieve this mission, my goal is to evaluate the current evidence on Casein Phosphopeptide - amorphous calcium phosphate (CPP-ACP), clarify its remineralizing capacity in early caries lesions, and shed light on non-invasive strategies for managing molar-incisor hypomineralization (MIH).

2.2. Scientometrics

Number of all publications:	10
Cumulative IF:	29.0
Av IF/publication:	2.90
Ranking (SCImago):	D1: 3, Q1:4, Q2:3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	5.9
Av IF/publication:	2.95
Ranking (Sci Mago):	D1:-, Q1: 2
Number of citations on Google Scholar:	59
Number of citations on MTMT (independent):	28
H-index:	4

The detailed bibliography of the student can be found on pages 65-68.

2.3. Future plans

After finishing my PhD, I will continue my scientific development. We have an accepted research proposal, “Understanding oral health inequalities and financing across Europe,” from EUROSTAT- Academia Europaea. I plan to continue investigating remineralization strategies for caries and MIH in the clinical setting. Furthermore, I would like to continue

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my work with PhD students as a supervisor and dedicate to my career at the Centre for Translational Medicine.

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3. SUMMARY OF THE THESIS

Dental caries and molar-incisor hypomineralization (MIH) are significant global health challenges, impacting over 30% and 13% of the global population worldwide. Despite recent advances, the efficacy of early management using non-invasive strategies remains unclear. Caries can progress to cavitation if untreated, requiring invasive treatment and increasing the risk of tooth loss. Similarly, MIH-affected enamel is porous, less mineralized, and prone to breakdown, complicating treatment and prognosis. Hypersensitivity, affecting nearly half of MIH patients, adds further challenges. This research investigates the efficacy of remineralizing agents, such as fluoride and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), in managing these conditions.

Study I evaluated the combined efficacy of CPP-ACP and fluoride compared to fluoride alone in managing white spot lesions (WSLs). Study II examined CPP-ACP and other agents for remineralizing MIH lesions and reducing hypersensitivity. Both studies used fluorescence-based and visual assessment methods to analyze outcomes. Study I found that CPP-ACP combined with fluoride did not significantly outperform fluoride alone in improving WSLs. Fluoride alone was effective in arresting or reversing early carious lesions. However, the certainty of evidence was very low, underscoring the need for high-quality studies to develop treatments that better complement fluoride in managing WSLs. In Study II, CPP-ACP was not significantly superior to fluoride in remineralizing MIH lesions but was more effective in reducing hypersensitivity. Other agents, such as silver diamine fluoride (SDF), calcium glycerophosphate (CaGP), and low-level laser therapy, showed mild-to-moderate effects on remineralization and hypersensitivity but lacked robust evidence due to heterogeneity and short follow-ups.

The findings from this research address critical knowledge gaps, providing insights into the limitations and potential of non-invasive strategies for managing caries and MIH. It impacts clinical decision-making and emphasizes the importance of tailored evidence-based approaches to improve patient outcomes, reduce the burden of invasive treatments, and guide future research toward establishing standardized clinical protocols.

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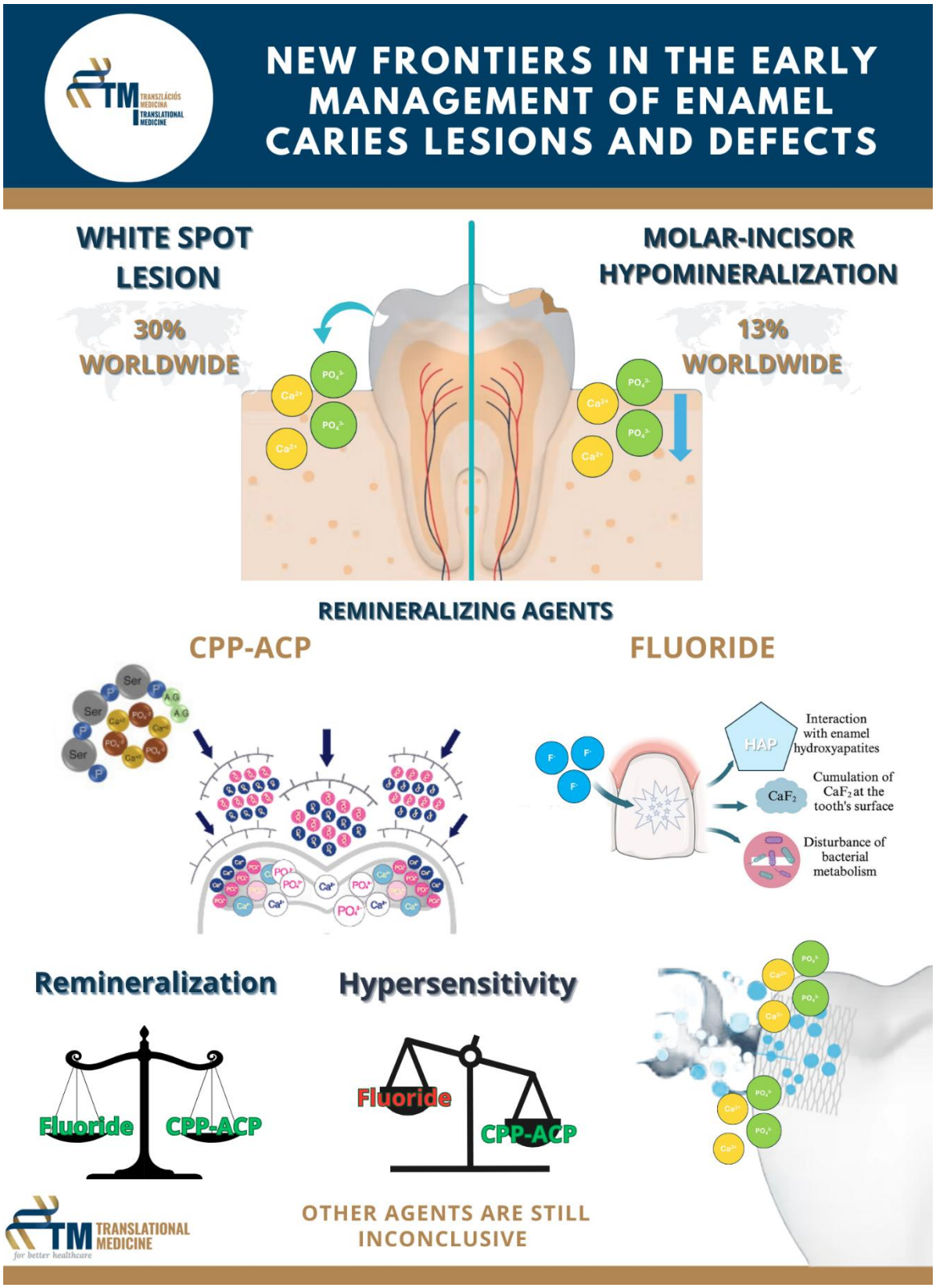
4. GRAPHICAL ABSTRACT



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5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

My topic investigates non-invasive strategies for managing enamel caries lesions and molar-incisor hypomineralization (MIH). Specifically, it evaluates the efficacy of remineralizing agents such as fluoride and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) in addressing demineralization and hypersensitivity associated with these conditions.

5.1.2. What is the problem to solve?

Despite the advances in preventive dentistry, the efficacy of early management strategies for early enamel caries lesions and MIH, including remineralizing agents, remains unclear. Enamel caries can progress to cavitation when not treated early, requiring invasive treatments and potentially leading to tooth loss. The hypomineralized enamel in MIH is more porous, less mineralized, and prone to breakdown, complicating treatment and prognosis. Hypersensitivity, which affects nearly half of MIH patients, increases clinical challenges. There is a lack of robust clinical evidence and standardized guidelines for the non-invasive management of enamel caries lesions. EAPD guidelines for MIH management offer only conditional recommendations. The goal is to provide evidence to improve early intervention and oral health outcomes for patients.

5.1.3. What is the importance of the topic?

Caries is the most common oral health condition, with over 2.3 billion people affected (1), while MIH affects around 13% worldwide (2). Their impact on oral health, aesthetics, and quality of life, particularly in children and adolescents, represents a public health concern. Early management strategies can help arrest the progression of lesions, prevent invasive treatments, and alleviate other associated functional and psychosocial burdens.

5.1.4. What would be the impact of our research results?

This research addresses critical knowledge gaps by systematically analyzing the efficacy of CPP-ACP and other non-invasive strategies for remineralization and hypersensitivity management of early caries lesions and MIH. The findings could inform clinical decision-making, improve patient outcomes, and ultimately lead to the development of standardized, evidence-based clinical protocols and guide future research.

5.2. Caries Process

Dental caries is a multifactorial disease resulting from complex dynamic interactions between pathological factors such as cariogenic bacteria, fermentable carbohydrates, and salivary dysfunction, and protective factors, such as antibacterial agents, sufficient saliva, and remineralizing ions (3, 4).

Despite the advancements over the last 20 years, the prevalence and incidence of dental caries have mainly remained the same (5). Therefore, understanding this dynamic disease process is essential to develop effective strategies to combat dental caries in clinical practice (6, 7), with individual management plans based on accurate diagnosis, including risk level, caries detection, assessment of caries severity, and activity (7).

Caries development consists of many alternating cycles of demineralization (mineral loss) and remineralization (mineral gain). Therefore, a constant balance between pathological and protective factors is needed to maintain oral health. The caries process will be initiated when an imbalance and net demineralization are sustained, resulting in mineral loss (8) (Fig.1.)

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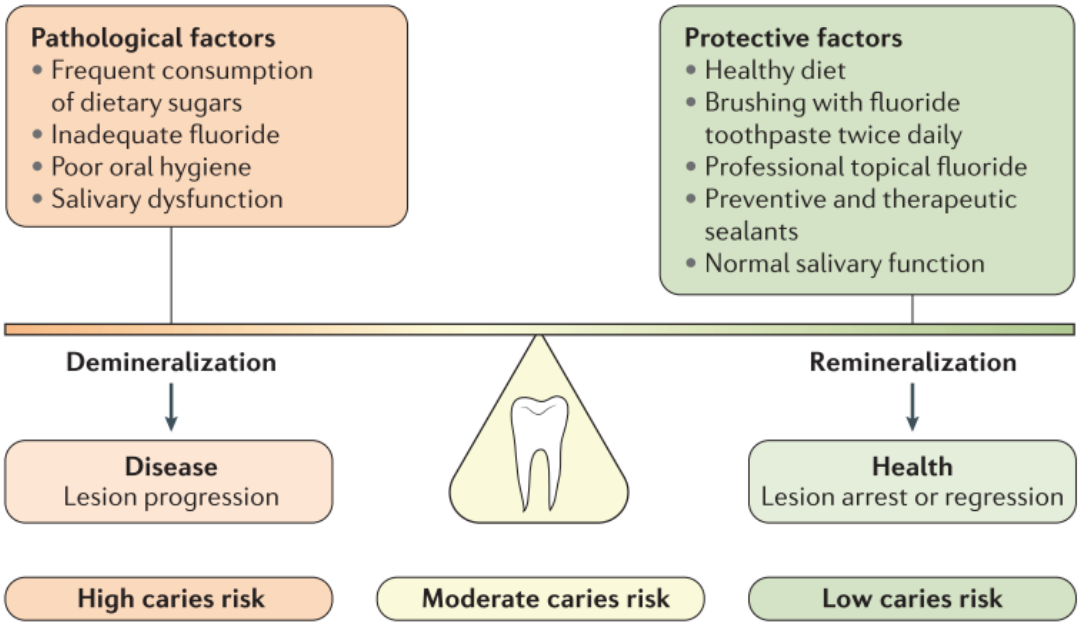

Figure 1: Caries Process by Pitts, Zero (8).

Cariogenic bacteria, primarily *mutans streptococci* and *lactobacilli* species, play a central role in this process. These bacteria metabolize dietary fermentable carbohydrates, primarily sugars, producing organic acids (mainly lactic acid) within biofilm that drop the pH level to a point where hydroxyapatite starts dissolving (critical pH 5.5). It partially demineralizes the surface layer of the tooth, increasing the porosity and allowing acids to diffuse into the subsurface. The enamel surface supersaturates from reaction product concentrations (calcium and phosphate) building up in the biofilm, stopping the demineralization process and favoring mineral reprecipitation. The acids diffusing from the biofilm do not react with the surface layer but continue deeper in the undersaturated subsurface, which could explain the higher rate of demineralization in subsurface enamel (8, 9).

As the rate of mineral loss becomes greater in the subsurface than at the surface, it may result in what is commonly referred to as a white spot (non-cavitated) lesion. These spots represent non-cavitated enamel incipient carious lesions with chalky-white enamel areas. The white opaque appearance of early enamel caries is caused by an optical phenomenon resulting from the mineral loss and increase in enamel porosity, which alters the internal reflection, surface roughness, and loss of brightness (10, 11).

White spot lesions are the first stage of dental caries, and if the demineralization process is not stopped, the intact enamel surface eventually collapses and cavitates (10). The progression from demineralization to cavitation is typically a slow process, occurring over months or years (8, 9), and when detected in its initial phase, lesions are subject to remineralization and could be arrested or reversed (4, 11).

5.2.1. Molar-Incisor Hypomineralization (MIH)

The term Molar-Incisor Hypomineralization was first introduced by Weerheijm, Jalevik (12) to describe a qualitative enamel developmental defect of systemic origin that affects one or more permanent molars, often involving incisors. Globally, the prevalence of MIH ranges from 2.8 to 40.2%, with most studies located in Europe (2, 13). This variability could be explained by the different diagnostic criteria used by researchers (14). A recent systematic review by Lopes, Machado (15) found a 13% overall prevalence of MIH, including only the European Academy of Pediatric Dentistry (EAPD) criteria (16).

Clinically, MIH hypomineralized enamel appears as demarcated opacities with defined borders from healthy enamel. The colors range from creamy-white in mild cases to yellow-brown in severe cases (17). Affected teeth often have structural loss associated with pre-existing demarcated opacity. Common clinical consequences of MIH are the presence of severe destruction in first permanent molars, atypical restorations, and dental extractions (18, 19). MIH-affected enamel has lower mineral density, hardness, and elastic modulus, as well as increased protein content and porosity, making it more susceptible to breakdown under masticatory forces, further complicating both treatment and prognosis (18, 20, 21). Severe lesions are commonly associated with post-eruptive enamel breakdown (PEB), susceptibility to caries, hypersensitivity, and aesthetic issues, and affect patients' socio-psychological well-being and quality of life (22, 23). Severely hypomineralized molars are at ten times greater risk of developing caries (24).

Dentin hypersensitivity (DH) affects 45% of patients with MIH (25), particularly in severe cases (26, 27). Managing DH in MIH patients is challenging due to their increased susceptibility to plaque accumulation and caries and compromised oral hygiene caused by the altered properties of MIH-affected enamel (28).

Approximately 27% of MIH-affected teeth have required or will require treatment at some point (29). Therefore, additional challenges, such as pain, anesthetic difficulties, dental anxiety, and behavior management issues, negatively impact their quality of life and make clinical management complex (30-33).

5.2.2. Understanding Fluoride Role in Remineralization

Remineralization is a key repair process for enamel caries and developmental enamel defects such as MIH. This process involves the deposition of calcium and phosphate ions into demineralized areas of enamel or dentin, sourced primarily from saliva. Saliva has numerous roles, including buffering the acid and facilitating the reprecipitation of mineral components (remineralization) since it is supersaturated with calcium and phosphate relative to hydroxyapatite. This will enhance resistance to further demineralization and maintain enamel integrity (34, 35).

In enamel caries, remineralization can occur naturally when dissolved mineral ions (Ca^{2+} and PO_4^{3-}) are deposited into crystal voids of the demineralized tooth structure, effectively restoring the structural integrity of the enamel. This process is greatly enhanced by free fluoride ions in oral fluid, allowing the incorporation of ions into hydroxyapatite, forming fluorhydroxyapatite or fluorapatite. These physicochemical alterations make it more resistant to acid dissolution than the original hydroxyapatite, making a remineralized enamel less susceptible to future cariogenic challenges. Fluoride is also effective at inhibiting demineralization when present in oral solution, and it adsorbs to the surface of crystals, protecting enamel against acid dissolution (4, 9, 35-37).

Research on remineralization underscores the importance of fluoride as the primary agent to enhance mineral uptake and inhibit demineralization. However, high caries-risk patients and populations often need adjunctive therapies to increase fluoride-mediated remineralization (4, 38). MIH, due to the enamel porosity and lower mineral content, presents additional challenges for remineralization (21).

Promising strategies to enhance remineralization would be to increase the availability of calcium and phosphate, particularly in inadequate salivary flow rate, and to ensure more efficient fluoride delivery over more extended periods (39). Remineralization strategies

for MIH-affected teeth should focus on both enhancing the mineral density of the weakened enamel and reducing associated hypersensitivity.

Among the available fluoride-based treatments, fluoride varnish increases caries resistance and also alleviates hypersensitivity by forming a temporary protective layer that slows demineralization and enhances fluoride uptake (40). Emerging treatments with promising results, such as silver diamine fluoride (SDF), are also being explored to manage MIH-related sensitivity (41). However, further studies are required to assess their long-term effectiveness.

5.2.3. Non-Fluoride Remineralizing Agents

New systems have been introduced in the last decades, such as non-fluoride enamel remineralizing agents and fluoride boosters, to increase the remineralizing potential of fluoride (4, 6, 42). Calcium phosphate systems have been developed to enhance the ability of fluoride to promote remineralization. The additional calcium phosphate ions can increase diffusion gradients, favoring fluoride ion-mediated remineralization and enhancing enamel subsurface remineralization (43).

Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) has been developed to promote that process by increasing the local bioavailability of Ca^{2+} and PO_4^{3-} ions (44, 45). Casein phosphopeptide (CPP) is based on casein, a milk protein that binds and chelates calcium, providing the basis for its calcium phosphate donor capacity (4, 43, 46, 47). CPP may serve as a saliva biomimetic compound with a great capacity of stabilizing calcium and phosphate, preventing the formation of poorly soluble phases and maintaining the bioavailability of ions to facilitate their precipitation on the enamel surface lesions and thus effectively inhibiting demineralization and enhancing remineralization (48-51). The binding between CPP-ACP is pH-dependent. As expected, the binding is decreased at lower pH, while higher pH prevents spontaneous precipitation of calcium phosphate (52, 53). Therefore, this material has been suggested to be particularly effective in the remineralization of early enamel lesions and the treatment of other enamel defects (51, 52, 54, 55).

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6. OBJECTIVES

6.1. Study I – Investigating the efficacy of CPP-ACP on remineralization of white spot lesions compared to fluoride therapies alone

We aimed to evaluate the current evidence on CPP-ACP systematically and to provide clarification on its remineralizing capacity. Therefore, we investigate whether the combination of CPP-ACP and topical fluoride has superior effects on remineralizing early carious lesions compared to fluoride alone. We hypothesized that CPP-ACP combined with fluoride would be more effective in promoting remineralization when measured through fluorescence-based and visual methods.

6.2. Study II– Investigating non-invasive strategies for the management of hypersensitivity and remineralization of Molar-Incisor Hypomineralization (MIH) teeth

Our overall goal was to update and contextualize recommendations for non-invasive strategies for managing MIH. We aimed to understand which non-invasive strategy (CPP-ACP, fluoride, calcium glycerophosphate, silver diamine fluoride, low-level laser, and others) is the most effective for remineralization and hypersensitivity reduction in teeth affected by MIH. We hypothesized that CPP-ACP would be the most effective agent for increasing mineral content and reducing hypersensitivity.

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7. METHODS

Studies I and II complied with the guidelines described in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 recommendations (56). Additionally, our study protocols were registered at the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42021286245 and CRD42022321486 to ensure transparency. The PROSPERO registration can be accessed at https://www.crd.york.ac.uk/prospero/.

7.1. Study I. – Investigating the efficacy of CPP-ACP on remineralization of white spot lesions compared to fluoride therapies alone

7.1.1. Literature search and eligibility criteria

A comprehensive systematic literature search was conducted to identify relevant studies until October 17th, 2022, and three major databases were screened: Medline (PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). An extensive hand search in the reference lists of relevant articles and included records was also performed to find eligible records.

A well-defined search strategy combined two main domains - terms related to “caries” and “Casein phosphopeptide-amorphous calcium phosphate”. The detailed search key can be found in Cavalcante, Schulze Wenning (57). No filters or restrictions were applied during the search to allow for a comprehensive search.

Patients of any age diagnosed with early stages of carious lesions (P) who underwent treatment with CPP-ACP agents and fluoride used in combination were included (I). Any products containing CPP-ACP, such as paste, mousse, or varnish, including CPP-ACP with built-in fluoride (CPP-ACFP) and fluoride in different formulations (toothpaste, gel, and varnish) would be included. Studies should also contain a control group of fluoride therapies alone (C). The primary outcome (O) was remineralization potential measured by fluorescence-based methods – QLF and LF. Visual evaluation through visual change in lesion area (value obtained as the ratio between the total lesion and total surface area of teeth) was a secondary outcome (O).

Only randomized controlled trials (RCTs) were included to allow for the highest level of evidence. Studies were excluded when trials had no fluoride-only control group and when unbalanced intervention and control group could directly or indirectly influence outcome variables. Furthermore, patients with any associated developmental defects of enamel or erosion would be excluded to avoid any confounding factors.

7.1.2. Study selection and data extraction

EndNote X20.2 (v.7) software (Clarivate Analytics, Philadelphia, PA, USA) was used to manage the records, and two independent authors performed the study selection. After duplicate removal, the remaining studies were screened by title, abstract, and full text. Cohen's kappa (58) coefficient was calculated to assess the agreement between the two reviewers, and if any disagreements remained after discussion, a third reviewer was consulted.

Two investigators extracted data from each eligible study using a standardized data collection form. When full texts were unavailable electronically, authors were contacted. The following data was collected from the eligible articles: title, first author, year of publication, country, study design, main findings, patient demographics, follow-up time, interventions, and outcomes (remineralization efficacy measurements by QLF and LF and visual assessments). If there were any inconsistencies, a third reviewer would be consulted, and if data was unclear, authors were also contacted for clarification. When uncertainties remained, data would not be used in the quantitative analysis.

7.1.3. Risk of Bias and Quality assessment

Rob 2 tool for randomized trials (59) was used to assess bias and was performed in duplicate by two independent reviewers (B.C. and A.W.). Disagreements were resolved through discussion, and when they were not possible, a third reviewer was consulted (G.V.). This tool has five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. They would be overall judged as the worst risk of bias in any of the domains: a 'low risk' of bias if all domains were at low risk, at 'some concerns' if at least

one domain raised some concerns but no high risk, and at 'high risk' if at least one domain was at severe risk (59).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence for each outcome (60, 61), and was performed independently by two authors. The following criteria were analyzed: study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias. RCTs start with a high level of evidence, which can be downgraded by one level for 'serious concerns' and two for 'very serious concerns' in each domain. Finally, the certainty of the evidence for each outcome will be graded as "high," "moderate," "low," or "very low."

7.1.4. Data synthesis and analysis

R-statistics software (ver. 4.1.1., Vienna, Austria) was used for the statistical analyses. Mean differences (MDs) or standardized MDs (SMDs) for continuous data were calculated to summarize the effect of treatment from each study. MDs would be used if outcomes were homogeneous, while SMDs would be utilized for non-homogeneous. 95% confidence intervals (CIs) were estimated using the restricted maximum-likelihood estimator. Random-effects models were used to combine the studies due to the existing clinical and methodological heterogeneity. After data collection, statistical heterogeneity was examined using the I^2 and $\chi 2$ statistics. Forest plots were used to display the measured effect sizes with their 95% CIs for all studies included.

7.2. Study II. – Investigating non-invasive strategies for the management of hypersensitivity and remineralization of Molar-Incisor Hypomineralization (MIH) teeth

7.2.1. Literature search and eligibility criteria

An extensive search was conducted in the MEDLINE(via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) in July 2023, with an update performed on July 8th, 2024, to ensure that most updated evidence was included. No additions or modifications were made to the search terms.

The search strategy used a combination of terms related to “molar incisor Hypomineralization” and current non-invasive strategies for MIH lesions. More details on the search key are found in Cavalcante, Mlinkó (62). To ensure a comprehensive search, no filters or restrictions were applied. Furthermore, the reference lists of pertinent studies and records were manually searched to identify further eligible records.

PICO framework was applied, where studies involving subjects under 18 years of age diagnosed with MIH according to any validated diagnostic criteria – EAPD (63), Ghanim (14), Weerheijm (64) – were included (P), with non-invasive remineralization and hypersensitivity management (I/C) interventions with at least one data point before and after the intervention. Remineralization potential was measured instrumentally through fluorescence-based methods: (1) Laser fluorescence (LF) measuring the enhanced fluorescence produced by the organic content of the lesion, (2) Quantitative light-induced fluorescence (QLF) to assess the degree of the lesion compared to the surrounding healthy tooth structure background fluorescence (O). Hypersensitivity management was a secondary outcome (O) measured instrumentally and visually through any validated pain outcome measure, such as the visual analog scale (VAS), SCASS, WBFS, and others.

We have included any *in vivo*, clinical, and observational studies for a more extensive evidence review. Studies were excluded if patients had associated enamel defects other than MIH (demarcated opacities, diffuse opacity, hypoplasia, amelogenesis imperfecta, dentinogenesis imperfecta, fluorosis) or erosion.

7.2.2. Study selection and data extraction

The study selection proceeded similarly to the description in 7.1.2. Study I.

When full texts were not available electronically, the necessary correspondence was made with the authors of the studies. Two investigators (B.C. and É.M.) performed the data collection separately using a standardized data collection form, which the following items: title, first author, year of publication, country, study design, number of patients and teeth, main findings, patient demographics, type of intervention, outcome measures for remineralization efficacy, and hypersensitivity. Lesion severity was categorized according to the EAPD criteria (Table 1). Quantitative analyses used teeth as the unit of measurement, and where multiple follow-ups were reported, data closest to the 3-month

mark were analyzed to allow for a more homogeneous dataset. In cases with more than one publication on the same cohort of patients, data was extracted from each report separately, and information was combined. Discrepancies were resolved by a third independent reviewer when necessary (G.V.).

Table 1. Description of severity level according to the EAPD criteria (described by Lygidakis et al., 2022).

Severity level	Signs and symptoms
Mild	Demarcated enamel opacities without enamel breakdown
	Induced sensitivity to external stimuli, e.g., air/water but not brushing
	Mild aesthetic concerns on discoloration of the incisors
Severe	Demarcated enamel opacities with breakdown and caries
	Spontaneous and persistent hypersensitivity affecting function, e.g., brushing, mastication
	Strong aesthetic concerns that may have a socio-psychological impact

7.2.3. Quality assessment

For non-randomized studies, ROBINS-I tool (65) was applied to assess through seven domains: bias due to confounding, bias due to participant selection, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported results. The categories for judgments were: ‘low risk’ when all domains were judged as low risk; ‘moderate risk’ when all domains were at low or moderate; ‘serious risk’ if at

least one domain was at serious risk, and ‘critical risk’ when at least one judgment was critical.

For randomized controlled trials, the ROB 2 tool (59) was used, including five domains: bias from the randomization process, deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of results reported. The judgment was performed similarly to ROBINS-I, except for the critical risk of bias category, which was not present.

Two independent authors conducted both assessments (B.C. and É.M.), and disagreements were addressed through discussions, reviewing the study details, or consulting a third reviewer.

7.2.4. Data synthesis and analysis

A random-effects model was used due to the expected substantial heterogeneity across studies regarding interventions, outcome measures, and patient characteristics. Mean differences (MD) were expressed as an effect size measure with 95% confidence intervals (CIs). The sample size, mean, and corresponding standard deviation (SD) were extracted from each study to calculate study MDs and pooled MDs. The mean values of the control group were subtracted from the mean values of the experimental group.

For hypersensitivity, outcome measures from varying scales were standardized to a standard 0–10 scale to ensure comparability, and MD was used. The VAS and the WBFS scales were not modified (0-10), while SCASS (0–3) and VAS Pimenta (0–4) scores were multiplied by 3.33 and 2.5, respectively. While this approach facilitates comparability, it assumes linear relationships between scales and that the conversion factor is applicable across all studies with proportional changes, potentially introducing bias and not capturing subjective pain differences.

The inverse variance weighting method was used to pool mean values and MD. Heterogeneity variance (τ^2) was estimated using the restricted maximum likelihood method, with Q-profile methods providing confidence intervals (66, 67). The t-distribution-based method was used for the CI of MD calculations of individual studies.

The Hartung–Knapp adjustment was applied to improve the robustness of CIs for MDs (68, 69).

A fixed-effects “plural” model (mixed-effects) was utilized for subgroup analysis, following the recommendations of (70). We did not expect substantial between-study heterogeneity differences across subgroups, and the number of studies was relatively small, so a standard $\tau 2$ value was assumed. Differences between subgroups were tested using the Cochrane Q (omnibus) test (66). The null hypothesis was rejected at a 5% significance level. Due to the inclusion of fewer than ten studies in each analysis, statistical funnel plot asymmetry tests were not performed (71). Instead, potential publication bias was assessed qualitatively by examining study characteristics, trial registries, and selective outcomes reporting.

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8. RESULTS

8.1. Study I. – Investigating the efficacy of CPP-ACP on remineralization of white spot lesions compared to fluoride therapies alone

8.1.1. Search and Selection

The systematic search yielded 1,497 related records, and after duplicate removal, 973 records remained and were screened by title and abstract. Based on the eligibility criteria, 44 items were selected for full-text review. Twenty-one RCTs were finally eligible for qualitative synthesis, with fifteen included in the quantitative synthesis. The PRISMA flow diagram summarizing all stages of the selection is presented in Figure 1.

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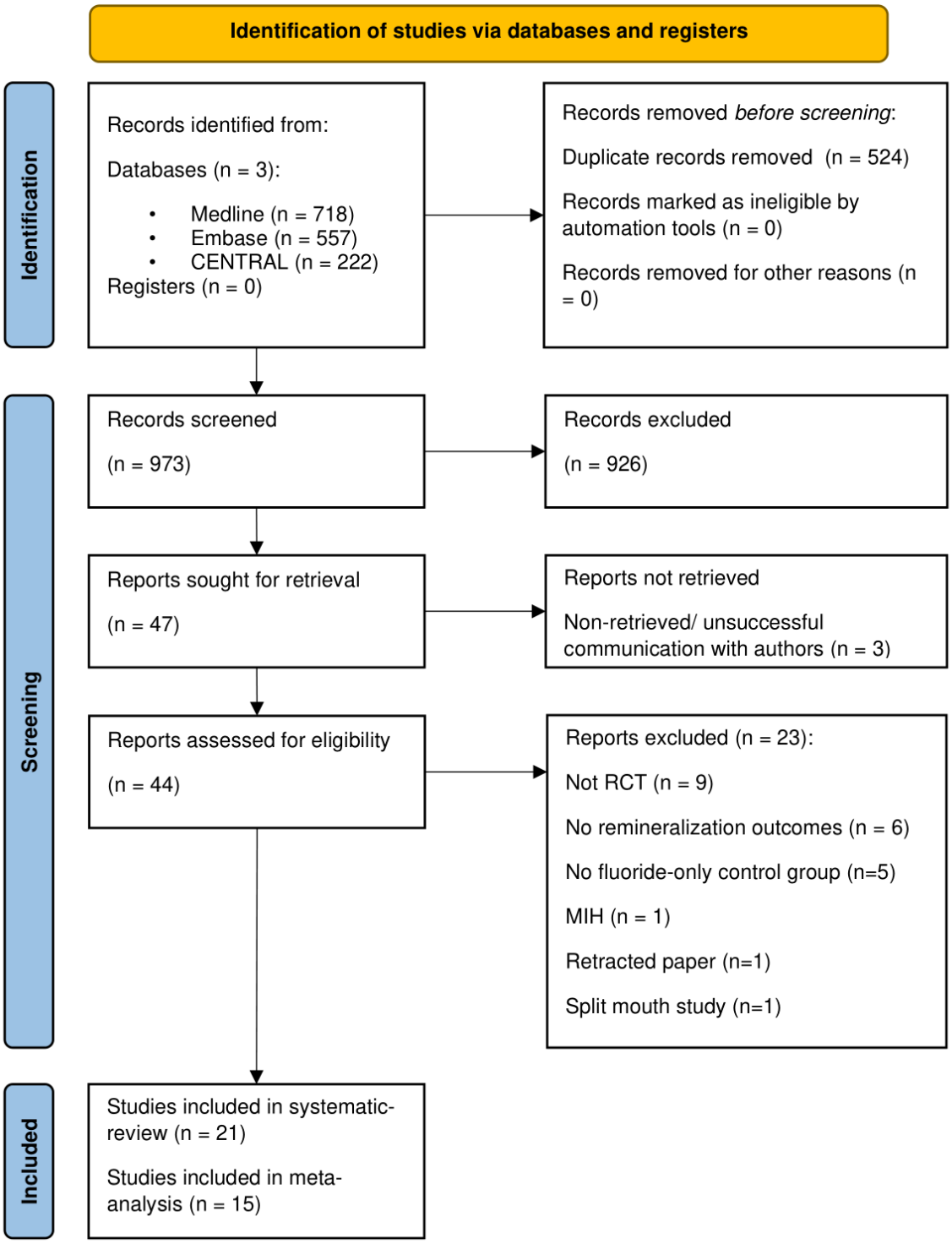

Figure 1. PRISMA flowchart illustrating the study selection process (57).

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8.1.2. Description of the Included Studies

The primary characteristics of the included studies are detailed in Table 2. These RCTs were conducted between 2010 and 2021 and involved participants aged 2 to 35. The studies were performed in various countries, including Jordan, The Netherlands, Denmark, Mexico, Turkey, Iran, Spain, Egypt, Brazil, India, and Thailand. Participants presented early-stage carious lesions, specifically white spot lesions (WSLs) of either orthodontic or non-orthodontic origin, and were evaluated for remineralization outcomes.

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Table 2. Characteristics of randomized controlled trials (RCTs) included in statistical analysis.

Author, year	Country	Sample (mean age; range - years)	Follow-up (months)	CPP-ACP + Fluoride		Fluoride Group		Main Outcome
				Type of combination	Frequency	Type of combination	Frequency	
Al-Batayneh, 2020 [1]	Jordan	114 (4.5)	6	Tooth Mousse + FT[1]	bid + bid	Ft [1]	bid	QLF
Beerens, 2010 [2]	The Netherlands	54 (15.5)	3	MI Paste Plus + FT	qd + bid	Control Paste+ Ft[2]	bid + qd	QLF
Beerens, 2018 [3]	The Netherlands	51 (15.32)	12	MI Paste Plus + FT	qd + bid	Control paste+ Ft[2]	bid + qd	QLF
Bröchner, 2011 [4]	Denmark	50 (15.2)	1	Tooth Mousse + FT [3]	qd + qd	Ft [3]	bid	QLF
Esparza-Villalpando, 2021 [5]	Mexico	84 (3-7)	1	MI Paste Plus + Ft [4]	bid + bid	Ft [4]	bid	LF (DIAGNOdent ™ Pen, model 2190, KaVo Dental,

								Biberach, Germany)
Güclü, 2016 a [6]	Turkey	21 (8-15)	3	Tooth Mousse + NaF Varnish	bid + 5 times in 12w	NaF Varnish	5 times in 12w	LF (DIAGNOdent ™ Pen, model 2190, KaVo Dental, Biberach, Germany)
Güclü, 2016 b [7]	Turkey	21 (8-15)	3	Tooth Mousse + Ft [4]	bid + bid	Ft[4]	bid	LF (DIAGNOdent ™ Pen, model 2190, KaVo Dental, Biberach, Germany)
Heravi, 2018 [8]	Iran	24 (16)	3	MI Paste Plus + Ft [5]	qd + bid	Ft[5]	bid	LF (DIAGNOdent)
Llena, 2015 a [9]	Spain	60 (6-14)	3	MI Paste Plus + Ft [6]	qd + n.r.	NaF Varnish + Ft[6]	monthly + n.r.	LF (DIAGNOdent,

								Kavo, Biberach, Germany)
Llena, 2015 b [10]	Spain	60 (6-14)	3	Tooth Mousse + Ft[6]	qd + n.r.	Control Paste +Ft[6]	qd + n.r.	LF (DIAGNOdent, Kavo, Biberach, Germany)
Mekky, 2021 [11]	Egypt	44 (3-5)	6	MI Varnish + Ft	3 times in 6 months + bid	NaF Varnish + Ft	3 times in 6 months + bid	LF (DIAGNOdent, Kavo, Biberach, Germany)
Memarpour, 2015 [12]	Iran	140 (21.2*)	12	Tooth Mousse + FT	bid + bid	Ft	qd	Mean/Median % WSL area
Mendes, 2018 a [13]	Brazil	36 (5-13)	3	MI Paste + FT	w + bid	Placebo paste + Ft	bid + n.r.	LF (DIAGNOdent ™ Pen, model 2190, KaVo Dental, Biberach, Germany)

Mendes, 2018 b [14]	Brazil	36 (5-13)	3	MI Paste Plus + FT	w + bid	Fluoride gel + Ft	bid + n.r.	LF (DIAGNOdent ™ Pen, model 2190, KaVo Dental, Biberach, Germany)
Radha,2020 [15]	India	60 (3-6)	6	MI Varnish + FT	qd + qd	NaF Varnish + Ft	n.r. + qd	Mean/Median % WSL area
Singh,2016 [16]	India	41 (16-25)	6	Tooth Mousse Plus + FT [7]	bid + bid	Ft[7]	bid	LF (DIAGNOdent, Kavo, Biberach, Germany); Mean/Median % WSL area
Sitthisettapong,2015 [17]	Thailand	79(37.51*)	12	Tooth Mousse + FT [7]	qd + qd	Placebo paste + Ft[7]	qd + qd	QLF
Yazicioglu, 2017 [18]	Turkey	30 (18-30)	1	MI Paste Plus + FT [4]	qd + bid	Ft[4]	bid	LF (DIAGNOdent Type 2095, Sn

													05-1519775; Kavo, Biberach, Germany)

Legends:*age in months, not years. “qd” means “once daily”, “bid” means “twice daily”, “w” means “weekly”, “LF” means the value of “laser fluorescence”, ”QLF” means the value of “quantitative light-induced fluorescence”, “Ft” means “Fluoride toothpaste”, “NaF” means “ Sodium Fluoride”. [1]Colgate Anti-cavity for kids (Sodium Fluoride 500ppm). [2]Fluoride-free control paste + calcium (Ultradent). [3] Colgate (Sodium Fluoride 1100 ppm). [4]Colgate Total (Sodium Fluoride 1450 ppm). [5]Crest Cavity Protection (Sodium Fluoride 1100 ppm). [6] Not specified, (Sodium fluoride 1100 ppm); [7]Colgate total® (Sodium Fluoride 1000 ppm).

MI Paste Plus contains 10% CPP-ACP + sodium fluoride 900 ppm; Tooth Mousse Plus contains 10% CPP-ACP + sodium fluoride 900 ppm. Tooth Mousse contains 10% CPP-ACP. MI Varnish contains 10% CPP-ACP + 5% sodium fluoride. These are trademarks of products. NaF varnish contains 5% sodium fluoride. Fluoride gel contains 1.23% acidulated phosphate fluoride.

The intervention in all studies involved CPP-ACP as the remineralizing agent. CPP-ACP was administered in combination with fluoride, either as part of the same product (e.g., CPP-ACFP, such as Tooth Mousse Plus or MI Paste Plus) or as CPP-ACP alone, with supplemental fluoride application via toothpaste, gels, or varnishes. In all studies, participants used fluoridated toothpaste for daily oral hygiene. Intervention regimens and follow-up durations ranged from one month to twelve months. Mousse and paste formulations were self-applied by participants or caregivers daily, while varnishes were applied at intervals of weeks or months. Remineralization outcomes were reported in 15 studies comprising 888 participants. Assessment criteria included Laser Fluorescence (LF), Quantitative Light-induced Fluorescence (QLF), and percentage changes in the WSL area.

8.1.3. Quantitative Synthesis Results

Fifteen studies have provided sufficient data for the meta-analysis (47, 72-85).

8.1.3.1. Primary Outcome

- **Laser Fluorescence (LF) values (DIAGNOdent)**

Eight studies measured the remineralization potential of CPP-ACP using LF (DIAGNOdent and DIAGNOdent pen). LF uses a relative numerical scale from 0 to 99. According to Lussi, values 0-13 = no caries; values 14-20 = enamel caries; values > 20 = dentinal caries, and values > 30 operative care is recommended besides prevention (86, 87). Changes from baseline were obtained as SMDs.

Four studies (74, 77, 79, 81) included multiple intervention and control groups, and data were analyzed accordingly. Analyses at one, three, and six months revealed the following:

At one month, no statistically significant difference was observed between this group and fluoride-only (SMD −0.30, 95%CI: −0.64 - 0.04) (Fig.2). The SMD (−0.30) also does not indicate a clinically significant change. Heterogeneity was moderate to high ($p<0.01$, I^2 =63%), mainly due to different population characteristics, the origin of WSL (non-orthodontic/orthodontic), and frequency of application. Subgroup analysis for CPP-ACFP and CPP-ACP did not indicate significant differences (Fig. 2).

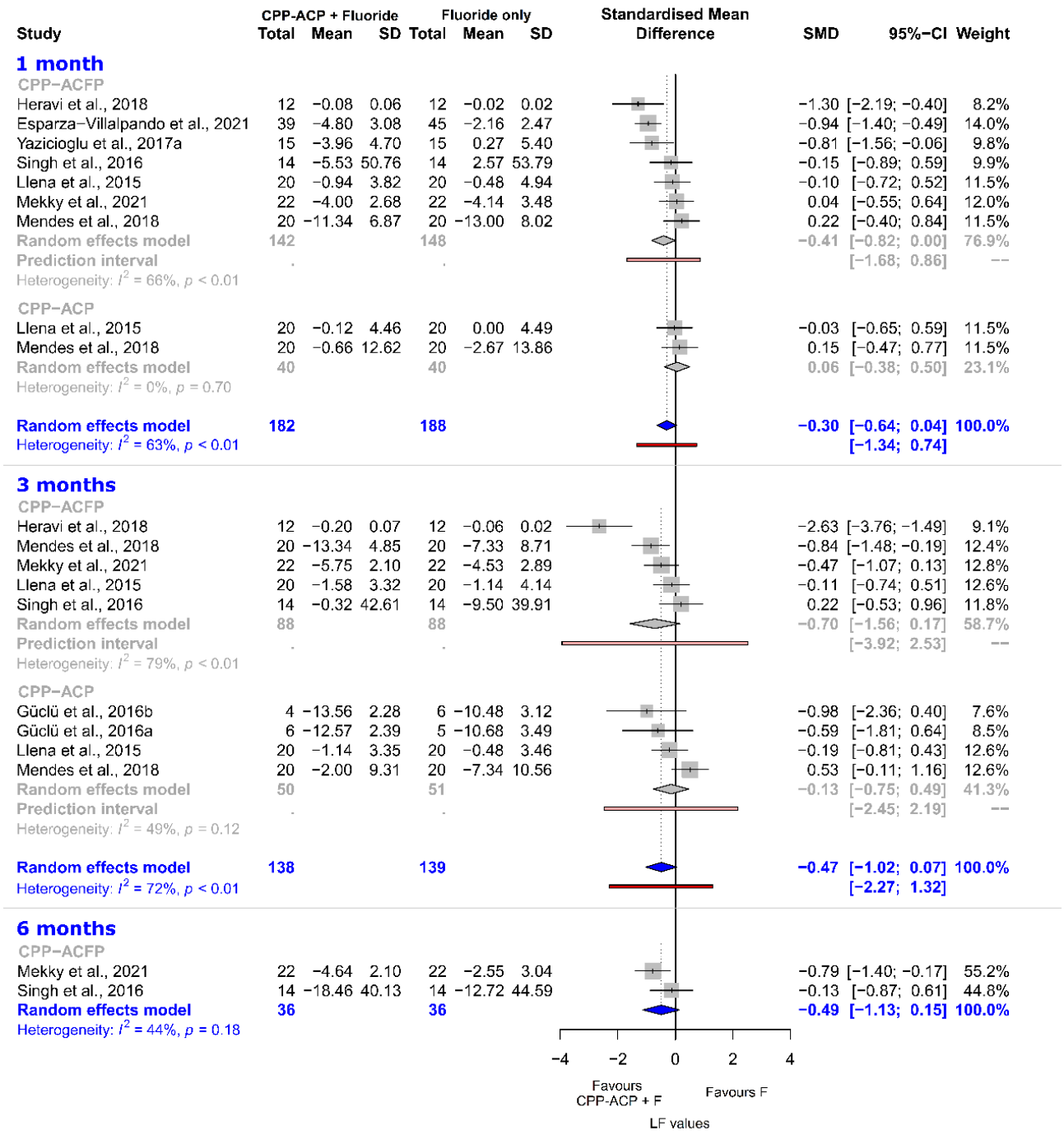

Figure 2. Forest plot of comparison of CPP-ACP + fluoride vs fluoride alone using LF values difference from baseline and 1, 3, and 6 months of follow-up (57).

At three months, no significant difference was observed between CPP-ACP and fluoride vs. fluoride alone (SMD −0.47, 95%CI: −1.02 - 0.07; I^2 =72%; p<0.01), even though two studies (81, 82) tended to favor the combined treatment group (Fig.2). Subgroup analysis of CPP-ACFP and CPP-ACP at three months did not provide significant information.

At six months, only two studies could be included. No statistically significant difference or clinical relevance was observed between the groups (SMD −0.49, 95% CI:−1.13 - 0.15; I^2 = 44%; p= 0.18) (Fig. 2).

- **Quantitative Light-induced Fluorescence (QLF) values**

Five studies (72, 73, 76, 80, 83) with 310 patients assessed remineralization using QLF, which measures both fluorescence loss ΔF (%) and lesion area (mm^2), corresponding to mineral loss. Changes from baseline were reported as MDs.

At one month, QLF ΔF did not demonstrate any significant difference between the two groups (MD 0.21, 95%CI: −0.30 - 0.71; I^2 = 0%; p=0) (Fig. 3). The heterogeneity was low among studies. At three months, there was a statistically significant difference favoring the fluoride group (MD 0.58, 95%CI: 0.25 - 0.91; I^2 = 0%; p=0), but the difference did not indicate clinically relevant remineralization (Fig.3). At six months (Fig. 3), no significant difference was found (MD 0.60, 95%CI: −1.70 - 2.90; I^2 = 48%; p= 0.67).

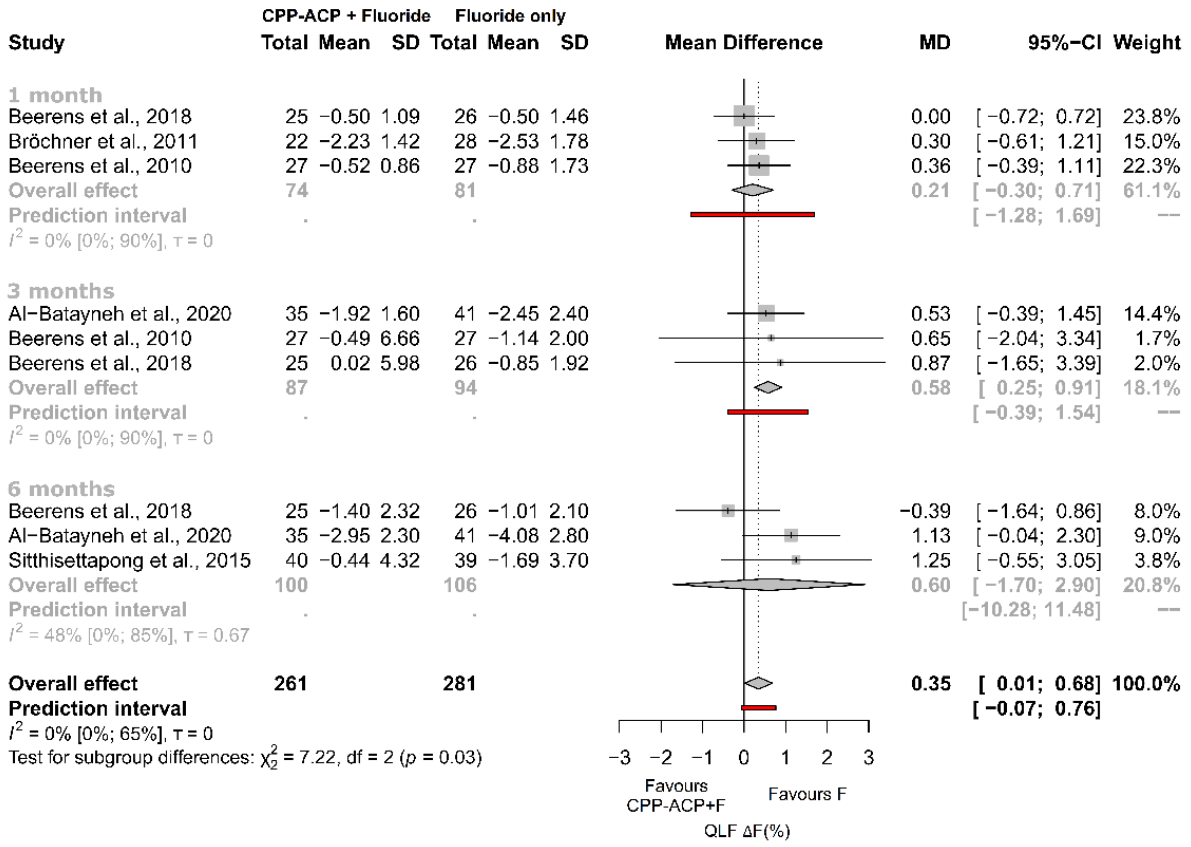

Figure 3. Forest plot of comparison of CPP-ACP + fluoride vs fluoride alone using QLF ΔF(%) values difference from baseline and 1,3 and 6 months of follow-up (57).

Similar to QLF ΔF(%), QLF area (mm^2) showed no statistically significant difference at either one month (SMD 0.11, 95%CI: −0.2 - 0.43; I^2 = 0%; p= 0.68), three months (SMD 0.13, 95%CI: −0.16 - 0.42; I^2 = 0%; p= 0.80), or six months (SMD 0.23, 95%CI: −0.04 - 0.51; I^2 = 0%; p= 0.42) (shown in Fig. 4).

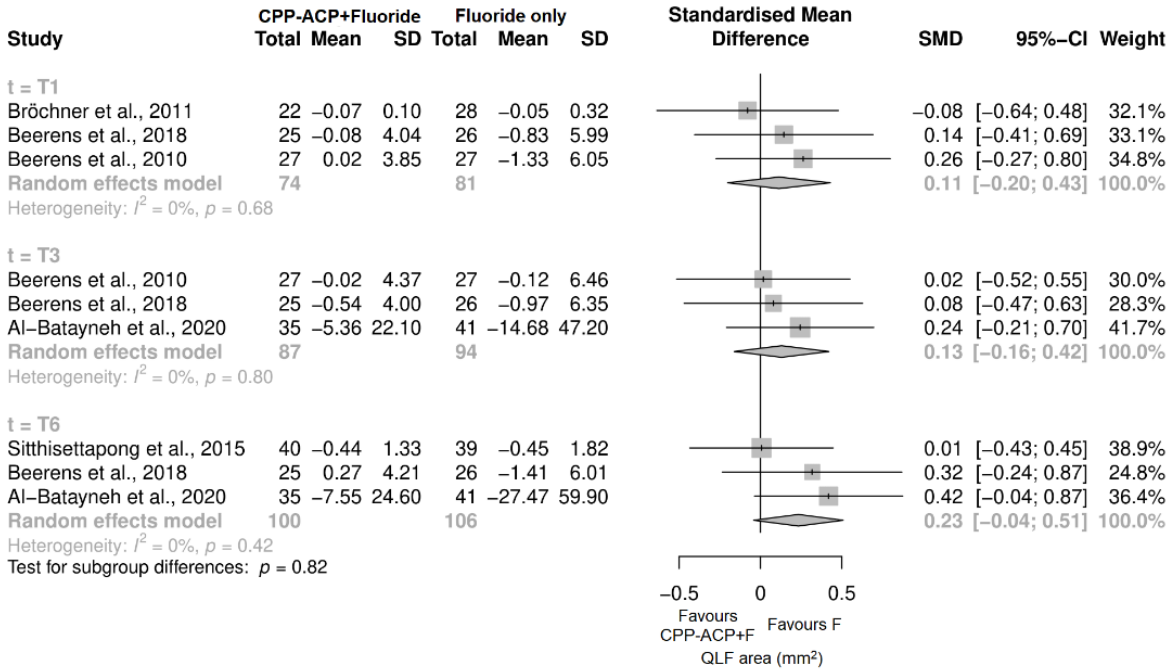

Figure 4. Forest plot of comparison of CPP-ACP + fluoride vs. fluoride alone using QLF area (mm^2) values difference from baseline and 1, 3, and 6 months of follow-up (57).

8.1.3.2. Secondary Outcome

- **Percent Change in WSL Area (%)**

The mean percent change in the WSL area was calculated based on the follow-up and baseline differences. Mean percent changes (%) were reported as SMDs.

At one (SMD −0.06, 95%CI: −0.54 - 0.41; I^2 = 0%; p= 0.78) and three months (SMD −0.24, 95%CI: −0.57 - 0.10; I^2 = 0%; p= 0.89), no significant differences were observed between the groups (Fig.5). At six months, a minor but statistically significant

improvement in the CPP-ACP plus fluoride group was observed (SMD −0.38, 95%CI: −0.72 - −0.04; I² = 0%; p= 0.62). However, the difference was not clinically meaningful.

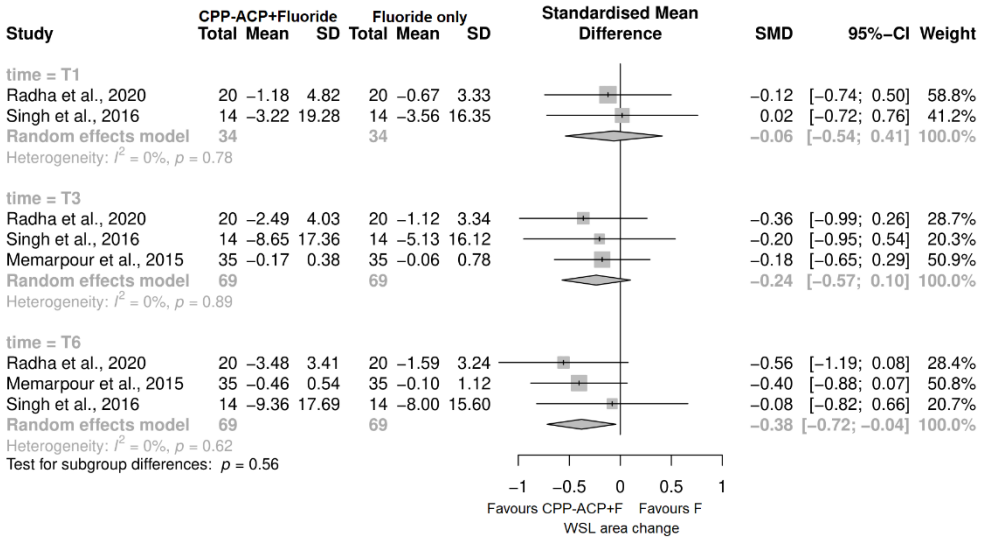

Figure 5. Forest plot of comparison of CPP-ACP + fluoride vs. fluoride alone using WSL visual area change (%) values from baseline and 1, 3, and 6 months of follow-up (57).

8.1.4. Risk of Bias Assessment

The Risk of Bias 2 Tool (59) was used. Out of 15 studies, five demonstrated an overall ‘low risk’; seven had ‘some concerns’, and three had a ‘high risk’ (73, 81, 83). Deviation from intended interventions and selection of reported results had the most ratings of ‘some concerns’ (eight and six, respectively) and ‘high risk’ (two studies each). In contrast, the randomization process and missing outcome data were mostly ‘low risk’. A detailed summary of the risk of bias is provided in Figure 6.

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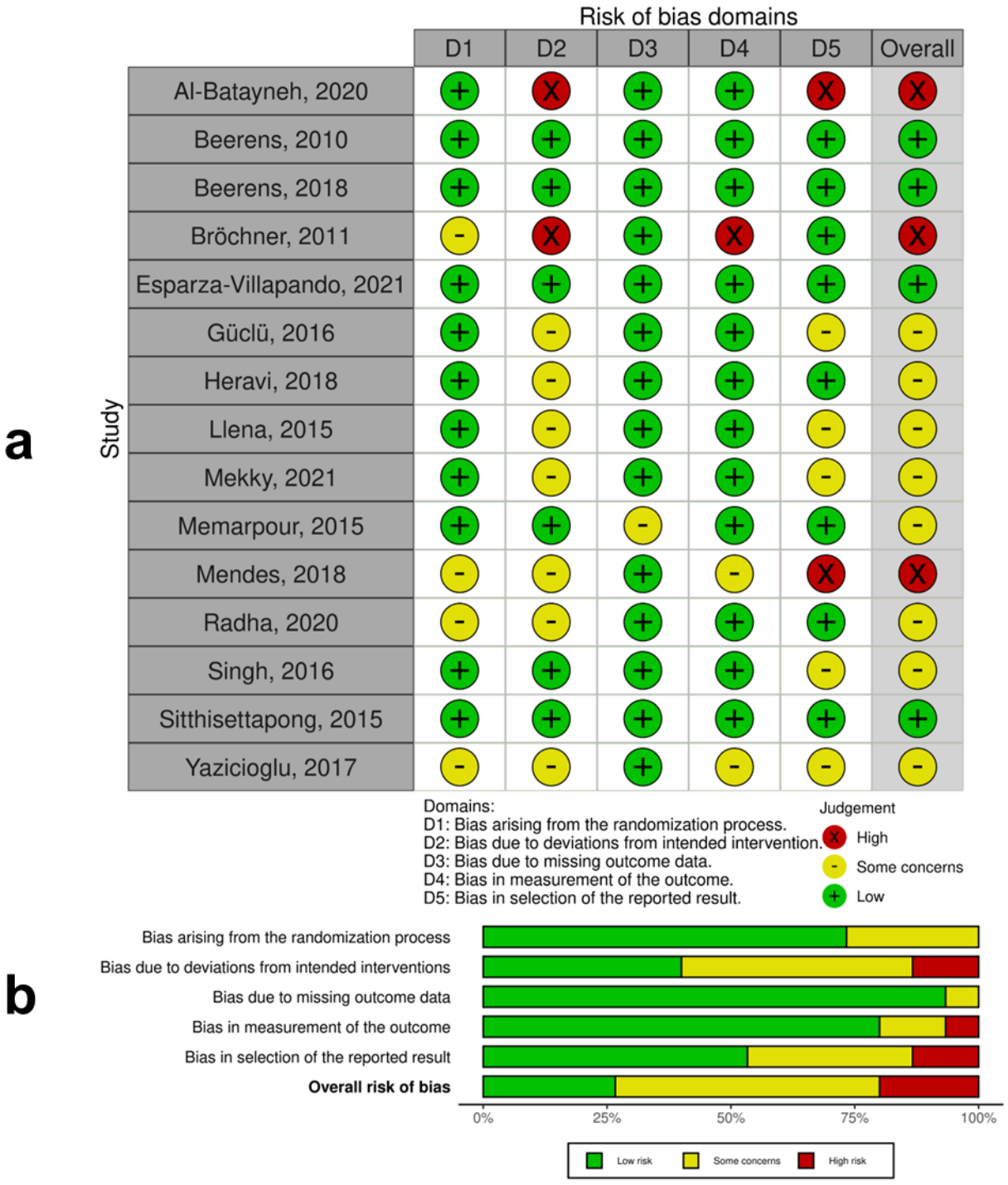

Figure 6. a) ROB 2 tool – risk of bias graph. Bias in each risk of bias item for each included study. **b)** Risk of bias graph. Percentage in each risk of bias item across included studies (57).

8.1.5. Certainty of evidence

The overall certainty of evidence, assessed using the GRADE approach, was rated very low. Limitations included the small number of studies, significant heterogeneity, risk of bias, imprecision, and limited patient numbers. Indirectness of outcome measures and wide confidence intervals further reduced certainty. Evidence of potential publication bias was noted in outcomes with few studies.

8.2. Study II. – Investigating non-invasive strategies for the management of hypersensitivity and remineralization of Molar-Incisor Hypomineralization teeth

8.2.1. Search and Selection

Our systematic search identified 1,566 records. Following duplicate removal, 1,103 went through title and abstract, and 22 items were eligible for full-text selection. Sixteen reports from 15 studies were included, with an additional study identified through reference screening. Thus, a total of 17 reports from 16 studies were considered. Of these, 15 studies were included in the quantitative analysis. The PRISMA flow diagram summarizing the selection process is shown in Figure 1.

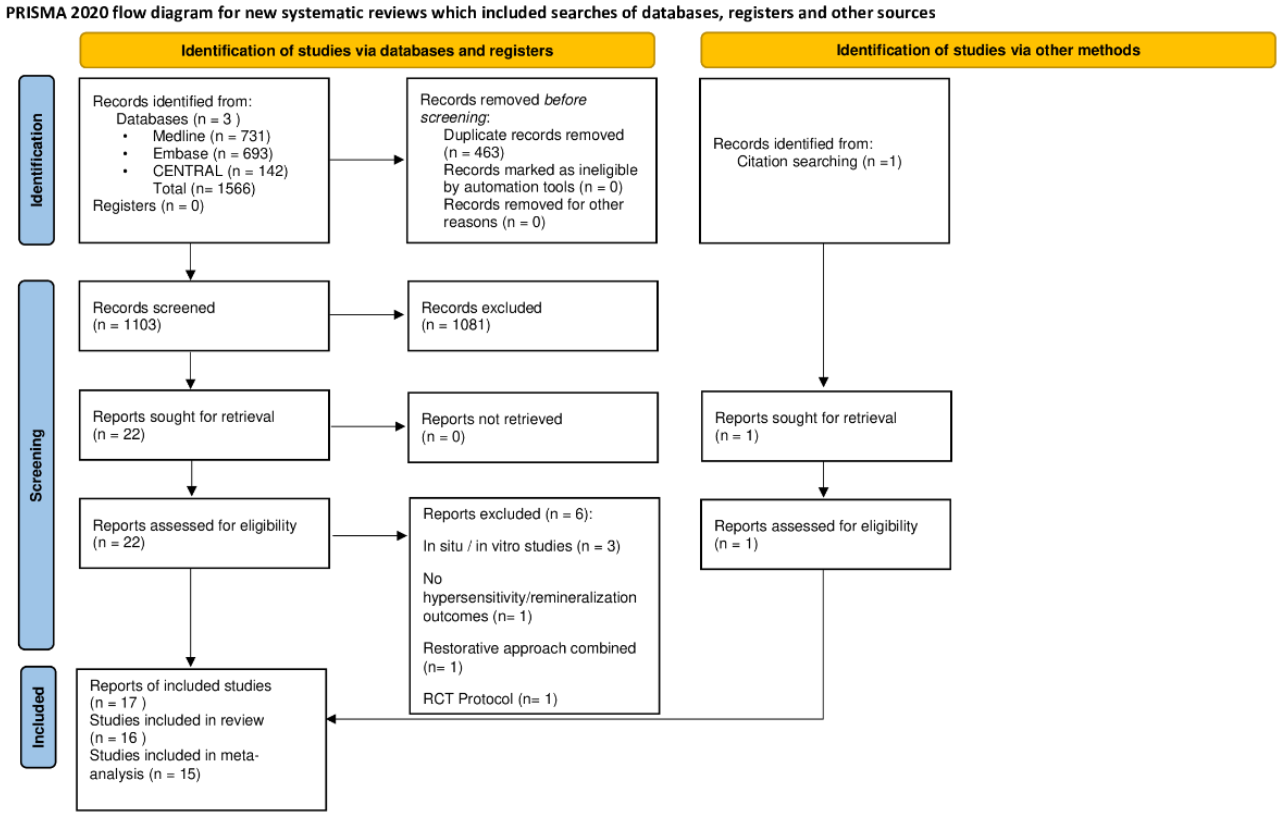

Figure 7. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the selection process (62).

8.2.2. Description of the Included Studies

The primary characteristics of the included studies are summarized in Table 1. In total, 15 studies involving 740 patients and 1,997 teeth were included. All studies published between 2016 and 2024 were randomized controlled and non-randomized trials or prospective cohort studies. Participants ranged in age from 3 to 17 years, and follow-up periods varied from 0.5 to 24 months. For the quantitative synthesis, a single data point closest to 3 months (within a range of 0.5 to 3 months) was selected to ensure homogeneity in the short-term analysis of treatment effects.

Table 3. Basic characteristics of the included studies in the systematic review and meta-analysis.

Study Design	Sample characteristics	MIH severity	Outcome measures	Interventions	Follow-up time points

Author (year), Country		Age range (mean ±SD)	Patients (drop-out)	Teeth	(criteria)			
Al-Nerabieah *et* al. (2024), Syria	RCT (Split-Mouth)	6–9 (7.6±1.4)	100 (0)	200	Mild (EAPD)	Caries development and activity: DMFT/ICDAS Post-eruptive Breakdown Hypersensitivity Airblast: SCASS	- CPP-ACPFV (Mi Varnish) - 38% SDF	T0: baseline T1: 3 months T2: 6 months T3: 9 months T4: 12 months
Bardellini *et* al. (2024), Italy	RCT	6-14 (9.5±2.7)	39 (0)	159	Mild and Severe (EAPD)	Hypersensitivity Airblast: VAS (WBFPS)	- CPP-ACFP (MI Paste Plus) +sham light therapy - Placebo mousse +PBMT - CPP-ACFP + PBMT	T0: baseline T1: after session T2: 7 days T3: 14 days T4: 4 weeks
Ballikaya *et* al. (2022)[a] and Erbas et al. (2024)[b], Turkey	RCT (Split-Mouth)	6-13 (8.8±1.5)	48 (3)	106	Mild (EAPD)	Hypersensitivity Airblast: SCASS Clinical Performance of sealants (USPHS)	- SDF; - SDF+ART (HVGIC)	T0: baseline[a] T1: 1 month[a] T2: 6 months[a] T3: 12 months[a] T4: 18 months [b] T5: 24 months [b] T6: 36 months [b]
Bakkal *et* al. (2017), Turkey	Prospective Cohort	7-12 (9.9±1.6)	54 (0)	38	Mild and Severe (N/R)	Remineralization: Laser Fluorescence (LF)	- 10% CPP-ACP - CPP-ACFP (10% CPP-ACP + 0.2% NaF - 900 ppm)	T0: baseline T1: 30 days
Bekes *et* al. (2017), Germany	Non-Randomized Trial	6-14 (8.2±1.9)	19 (3)	56 (12)	Mild and Severe (EAPD)	Hypersensitivity Airblast: SCASS Tactile: WBFS	- 8% arginine & calcium carbonate paste	T0: baseline T1: 1 week T2: 2 weeks T3: 4 weeks T4: 8 weeks
Biondi *et* al. (2017), Argentina	Prospective Cohort	6-17 (N/R)	56 (0)	92	Mild and Severe (N/R)	Remineralization: Laser Fluorescence (LF)	- 5% NaF varnish - 10% CPP-ACP crème - 5% NaF varnish + tricalcium phosphate (TCP)	T0: baseline T1: Day 15 T2: Day 30 T3: Day 45

Ehlers *et* al. (2021), Germany	RCT	6-11 (Group A 8.6±1.5; Group B: 8.4±1.2)	21 (7)	48	Mild and Severe (N/R)	Hypersensitivity Airblast (SCASS) Tactile (WBFS) Oral Hygiene (API) Rating of toothpaste taste (VAS)	- 10% Hydroxyapatite paste - Amine Fluoride toothpaste (1400 ppm)	T0: screening T1: baseline T2: 28±3 days T3: 56±3 days
Fütterer *et* al. (2019), Germany	Prospective Cohort	3-15 (8.5 [N/R])	78 (0)	218	Mild and Severe (EAPD)	Hypersensitivity Airblast (SCASS) Tactile (WBFS)	- Fluoride Varnish - Fissure sealant - Filling - Stainless Steel Crown (SSC)	T0:before T1: after (varying from 7 to 488 days)
Muniz *et* al. (2019), Brazil	RCT	8-12 (8.9±2.1)	66 (6)	214	Mild and Severe (EAPD)	Hypersensitivity Airblast (VAS Pimenta modified)	- Laser - 5% NaF varnish - 5% NaF varnish and laser	T0: baseline T1: 1 week T2: 2 weeks T3: 3 weeks T4: 4 weeks
Olgen *et* al. (2022), Turkey	RCT	6-9 (7.7±[N/R])	67 (18)	90	Mild and Severe (Weerheijm et al.)	Remineralization: Laser Fluorescence (LF) ICDAS	- 5% NaF Varnish - 10% CPP-ACP crème - CPP-ACFP (10% CPP-ACP + 0.2% NaF - 900 ppm) - Fluoride Toothpaste (1450 ppm)	T0: baseline T1: 3 months T2: 6 months T3: 9 months T4: 12 months T5: 15 months T6: 18 months T7: 21 months T8: 24 months
Özgul *et* al. (2018), Turkey	RT	7-12 (N/R)	33 (0)	92	Mild (N/R)	Hypersensitivity: Cold stimuli (VAS)	- 5% NaF Varnish - Ozone + 5% NaF Varnish - 10% CPP-ACP paste - Ozone + 10% CPP-ACP paste - CPP-ACFP - Ozone + CPP-ACFP	T0: baseline T1: 4 weeks T2: 12 weeks

Pasini *et* al. (2018), Italy	Prospective Randomized Trial	8-13 (N/R)	40 (0)	40	Mild and Severe (Weerheijm et al., 2003)	Hypersensitivity: Airblast (SCASS) Mechanical stimulus (VAS)	- Fluoride Toothpaste (1000 ppm) - 10% CPP-ACP paste	T0: baseline T1: 4 months
Restrepo *et* al. (2016). Brazil +	RT	9-12 (10.2±1.1)	51 (0)	51	Mild and Severe (EAPD)	Remineralization: Quantitative Light fluorescence imaging (QLF)	- 4 × applications 4% NaF varnish - Fluoride Toothpaste (1450 ppm)	T0: baseline T1: 4 weeks
Sezer *et* al. (2022), Turkey	RCT (Cross-over)	8-12 (9.2±1.4)	22 (0)	162	Mild and Severe (Weerheijm et al., 2003)	Remineralization: Laser Fluorescence (LF)	- CPP-ACFP (MI Paste Plus™) - CaGP (R.O.C.S.®)	T0: baseline 2 weeks lead-in T1: 12 weeks 2 weeks washout T2: 12 weeks
Sezer & Kargul, (2022), Turkey	RCT	8-12 (9.3±1.4)	53 (0)	401	Mild and Severe (Ghanim et al., 2015)	Remineralization: Laser Fluorescence (LF)	- CaGP (R.O.C.S.®) - CPP-ACFP (MI Paste Plus™) - Fluoride Toothpaste (1450 ppm)	T0: baseline T1: 1 month T2: 3 months
Singh *et* al. (2021). India	RT (Pilot Study)	8–14 (N/R)	30 (0)	30	Mild and Severe (Weerheijm et al., 2003)	Remineralization: Laser Fluorescence (LF)	- 5% NaF Varnish - 10% CPP-ACP paste	T0: baseline T1: 15 days

+ The study was not included in the quantitative analysis due to the different outcome measures (QLF) used from the other studies (LF). Legends: a: Ballikaya et al. (2022); ART: atraumatic restorative treatment; b: Erbas et al. (2024) b; CaGP: calcium glycerophosphate; CPP-ACP: casein phosphopeptide–amorphous calcium phosphate; CPP-ACFP: casein phosphopeptide–amorphous calcium fluoride phosphate; CPP-ACPFV: casein phosphopeptide–amorphous calcium phosphate fluoride varnish; DMFT: decayed, missing, and filled teeth; EAPD: European Academy of Pediatric Dentistry; HVGIC: high-viscosity glass ionomer cement; ICDAS: International Caries Detection and Assessment System; LF: laser fluorescence; MIH: molar–incisor hypomineralization; NaF: sodium fluoride; N/R: not reported; PBMT: photobiomodulation therapy; QLF: quantitative light-induced fluorescence; RCT: randomized controlled trial; RT: randomized trial; SCASS: Schiff Cold Air Sensitivity Scale; SDF: silver diamine fluoride; USPHS: United States Public Health Service; VAS: visual analog scale; WBFS: Wong-Baker Pain Rating Scale.

8.2.3. Quantitative Synthesis of Results

Fifteen studies provided sufficient data for the quantitative analysis (41, 88-103).

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8.2.3.1. Primary Outcome

- **Laser Fluorescence (LF) values (DIAGNOdent)**

CPP-ACP vs. Fluoride-based treatments

Six studies evaluated remineralization potential using laser fluorescence (LF), which measures fluorescence emitted from enamel on a relative scale (0–99). In the included studies, LF values were reported separately according to the lesion severity (mild or severe).

In Figure 8., no statistically significant differences and clinical relevance were observed between CPP-ACP and fluoride-based treatments (MD −3.80, 95% CI: −8.57 to 0.98). The χ^2 test ($\chi^2 = 2.12$, df = 2, p = 0.35) indicated low heterogeneity among studies, but the small number of studies limits the power to detect heterogeneity.

For mild lesions, no statistically significant differences were observed between the groups (MD −0.70, 95% CI: −1.45; 0.06, I^2 = 0% [CI: 0%, 90%]) (Fig.8.). Severe lesions exhibited a mean difference (MD) of −11.07 (95% CI: −25.46; 3.32, I^2 = 83% [CI: 47%, 97%]), suggesting a potential clinical effect of CPP-ACP on severe MIH lesions (Fig.8.). However, high heterogeneity and wide confidence intervals necessitate cautious interpretation of these results.

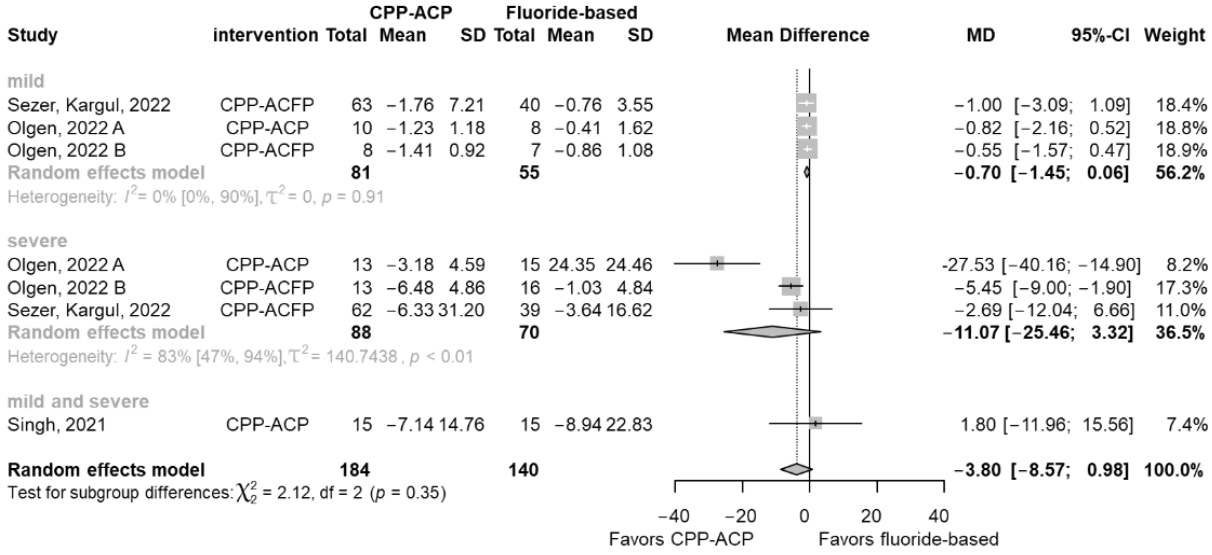

Figure 8. Forest plot comparing CPP-ACP vs fluoride-based group using the change from baseline LF values of MIH mild and severe lesions for remineralization (62).

Remineralization Strategies for Mild Lesions

Five studies reported four agents on mild MIH lesions in 435 teeth (Figure 9). Fluoride varnish showed the most significant reduction in LF values (mean −2.74, 95% CI: −5.91–0.43; I^2 = 60% [CI: 0%, 89%]) in 37 teeth, but the wider confidence interval results in less certainty in the effect size. CPP-ACP agents had a pooled mean reduction of −1.40 (95% CI: −1.84; −0.97; I^2 = 0 [CI: 0%, 71%]) in 190 teeth. CaGP showed a reduction of −1.04 in the LF scale in 160 teeth (mean −1.04, 95% CI: −2.34; 0.26; I^2 = 0). When fluoride toothpaste alone was used, a pooled mean reduction of −0.53 was found for 48 teeth (mean −0.53, 95% CI: −1.44–0.37; I^2 = 0). Overall, pooled effects were not clinically relevant, and findings should be interpreted cautiously.

Remineralization Strategies for Severe Lesions

Five studies reported four different agents on severe MIH lesions in 434 teeth (Figure 9). CaGP showed a reduction of −7.85 in the LF scale for 123 teeth (mean −7.85, 95% CI: −13.95–−1.76; I^2:57% [CI: 0%, 90%]), whereas fluoride varnish showed the greatest mean reduction in LF (mean −9.88, 95% CI: −24.18; 4.43; I^2:93% [CI: 60%, 95%]) for

45 teeth, however the low number of studies and wide CIs indicate less certainty in effect sizes.

CPP-ACP products showed a reduction of −4.83 (mean −4.83, 95% CI: −7.11; −2.55; I^2 :0% [CI: 0%, 79%]) in 131 teeth. The narrower CI indicates a more precise effect estimate. When fluoride toothpaste alone was used, an actual increase of 9.89 on the LF scale was found for 54 teeth (mean 9.89, 95% CI: −17.52; 37.31; I^2:93% [CI: 77%; 98%]). However, the wide confidence intervals should be considered for careful interpretation of results.

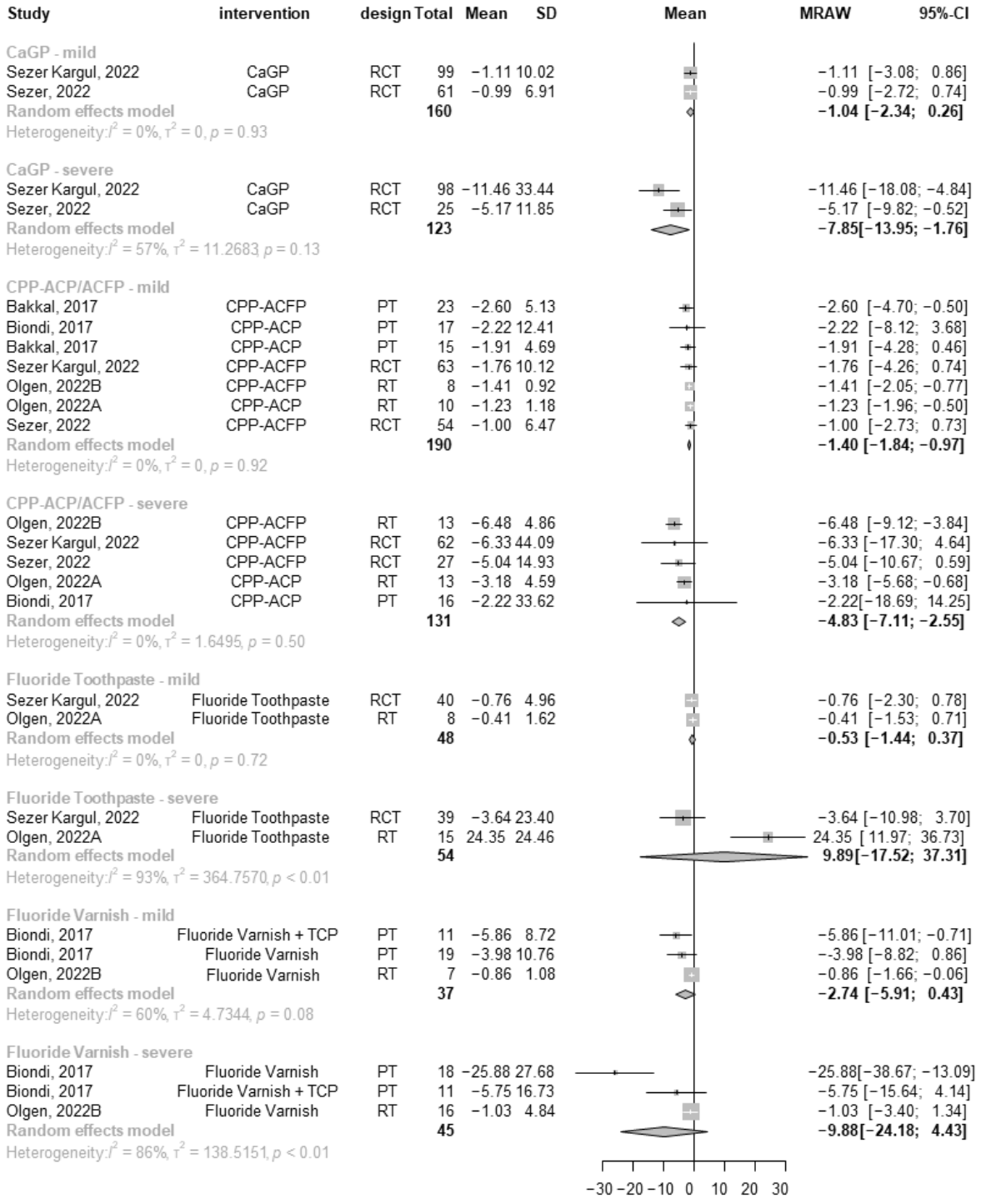

Figure 9. Forest plot presenting mean change from baseline LF values of different agents used for the remineralization of MIH mild and severe lesions (62).

8.2.3.2. Secondary Outcome

- **Hypersensitivity (visual pain scale)**

Hypersensitivity was measured on different pain scales and then standardized to 0–10 (104).

CPP-ACP vs. Fluoride Varnish

CPP-ACP significantly reduced hypersensitivity compared to fluoride varnish (MD −2.36, 95% CI: −3.83; −0.89), indicating a clinically relevant change.

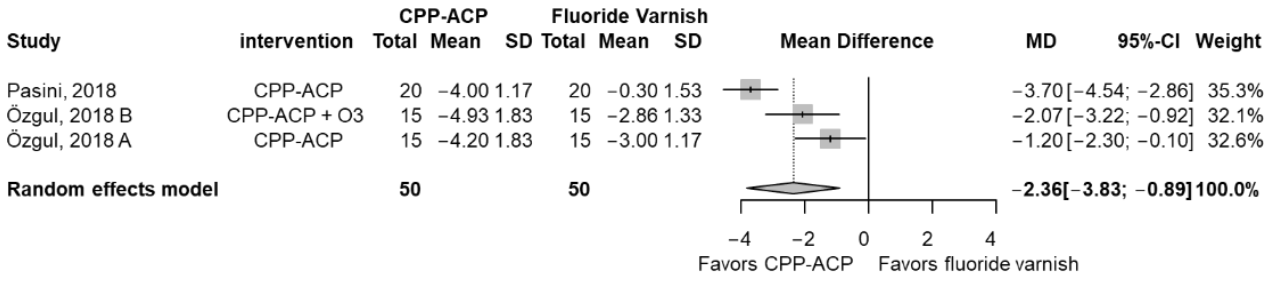

Figure 10. Forest plot comparing the CPP-ACP vs. fluoride varnish groups by changes in hypersensitivity compared to baseline, measured by the VAS pain scale (0 to 10), for MIH lesions (62).

CPP-ACP and Fluoride Varnish

Due to the heterogeneity of studies collected, no direct comparison could be made between different interventions, and effects were described for each arm.

Figure 5a shows a polled effect of −3.44 with CPP-ACP treatments (95%CI: −4.39; −2.49), indicating a clinically significant reduction in hypersensitivity for patients with MIH. CPP-ACP alone reduced hypersensitivity by −3.94 (95% CI: −4.46; −3.35), while CPP-ACP combined with ozone achieved a reduction of −3.66 (95% CI: −6.00; −1.32) (Fig. 5a). Fluoride varnish treatments found a mean reduction of −2.21 (95% CI: −3.49;−0.93; I^2:95%; $p < 0.01$) in 132 patients, and one of the studies had a combination of FV with ozone (mean −2.86, 95% CI: −3.87; −1.85) (Figure 5b).

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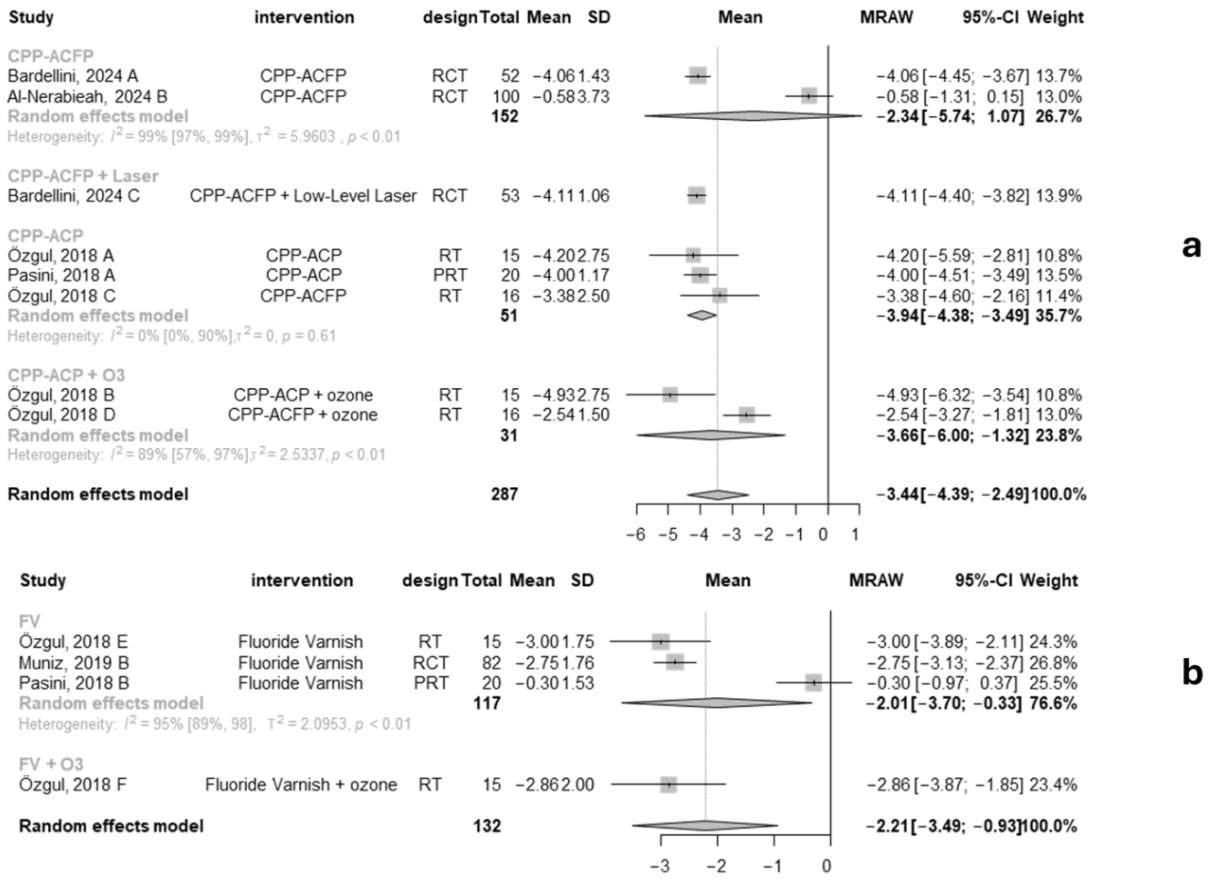

Figure 11. a) Forest plot presenting CPP-ACP (subgroups by CPP-ACP type): mean change from baseline values for hypersensitivity measured on VAS pain scale (0 to 10). b) Forest plot presenting fluoride varnish (subgroups by FV): mean change from baseline values for hypersensitivity measured on VAS pain scale (0 to 10) (62).

Hypersensitivity Management Agents

Six studies reported different interventions (amine fluoride toothpaste; arginine and calcium carbonate paste, hydroxyapatite paste, low-level laser, silver diamine fluoride) for hypersensitivity in MIH lesions (Fig.12.); however, since a few studies were included for each intervention, the plot is solely for visualization. Among these, low-level laser treatment showed the greatest reduction in hypersensitivity across 136 patients (mean −3.33, 95% CI: −4.47; −2.20) with narrow CIs.

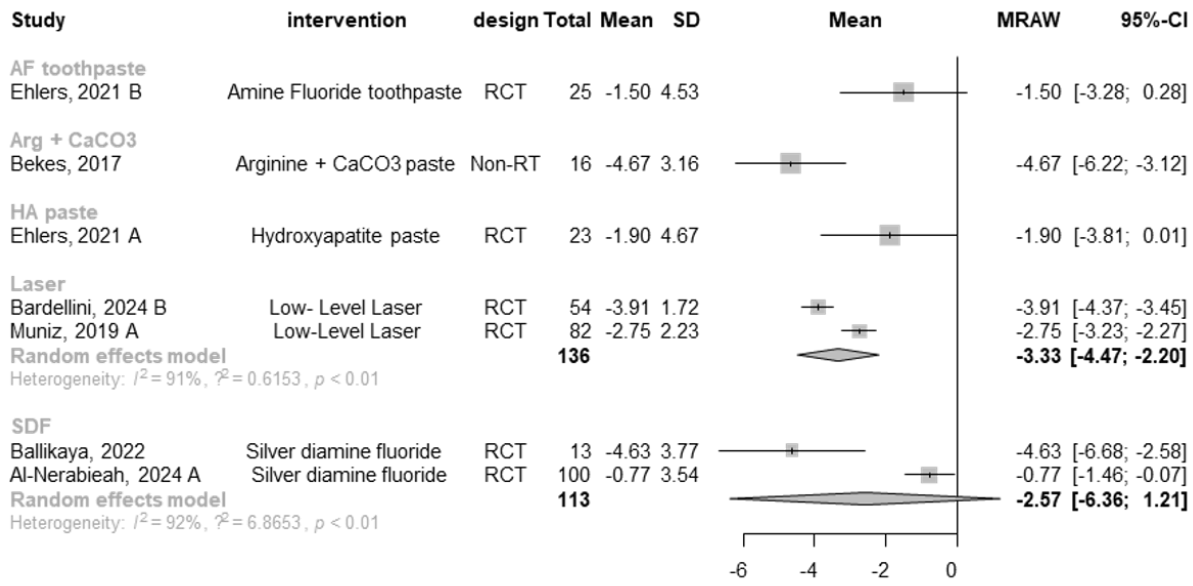

Figure 12. Forest plot presenting different agents for hypersensitivity: mean change from baseline values measured on VAS pain scale (0 to 10) (62).

8.2.4. Risk of Bias Assessment

Sixteen studies were assessed for the risk of bias. Four non-randomized studies evaluated using the ROBINS-I tool (Fig.13.a) were classified as having moderate (n = 3) or serious (n = 1) risk of bias, primarily due to participant selection and reporting biases. Serious bias was present in the selection of reported results only for one study, whereas one was moderate, and two were at low risk. All four studies were at moderate risk of bias due to the selection of participants and at low risk due to deviations from intended interventions.

Twelve RCTs were assessed with the ROB 2 tool (Fig.13.b). Six studies were at high risk, five at moderate risk, and one at low risk of bias. The risk of bias due to deviations from the intended intervention domain was serious for five studies, moderate in five, and low in two. On the other hand, the risk of bias due to missing outcome data was serious in one study and low in eleven. Two domains were not assessed for serious risk of bias, including bias in selecting the reported results (seven studies were assessed as moderate risk, and five as low risk) and bias from the randomization process (four at moderate risk, eight at low risk).

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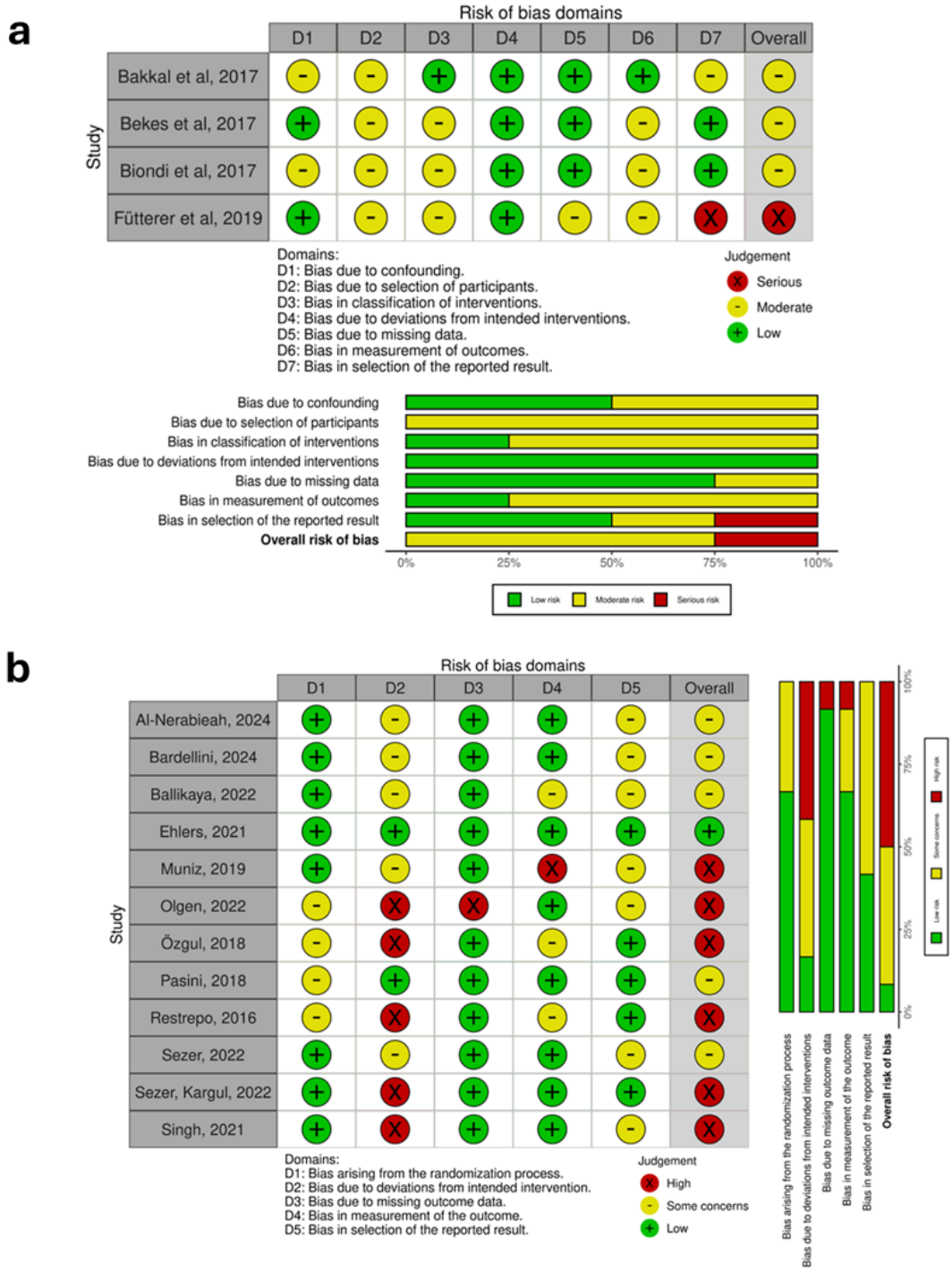

Figure 13. a) ROBINS-I tool – risk of bias summary: Bias in each risk of bias item for each included study. Risk of bias graph: Percentage of each bias item across included studies. **b)** ROB 2 tool – risk of bias summary: Bias in each risk of bias item for each included study. Risk of bias graph: Percentage of each bias item across included studies.

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9. DISCUSSION

9.1. Summary of findings, international comparisons

9.1.1. Summary of findings

Our Study I assessed the efficacy of CPP-ACP combined with fluoride (either in CPP-ACFP form or in separate CPP-ACP plus fluoride products) in ameliorating WSLs compared to topical fluoride-only treatments. The findings indicate that LF showed a tendency to favor CPP-ACP combined with fluoride over fluoride alone after one month of treatment in early carious lesions. However, this difference was not statistically significant. No difference was observed between the two groups at three and six months. QLF studies demonstrated a statistically significant advantage for fluoride alone in fluorescence loss (ΔF%) at three months, but no significant differences were observed at one or six months. These differences were minor and did not represent relevant clinical benefits. Similarly, QLF-based lesion area measurements (mm^2) showed no statistically significant differences between the two groups at any time point. Since fluorescence-based tools provide indirect measures of non-cavitated lesion improvement, these results should be interpreted cautiously and do not confirm a clear remineralization benefit of CPP-ACP.

In Study II, we assessed the effectiveness of non-invasive treatments for MIH, focusing on fluorescence-based remineralization and reduction in hypersensitivity. While CPP-ACP showed a modest improvement over fluoride-based treatments in remineralization measured by LF and QLF, the difference was not statistically significant, indicating a potential clinically relevant advantage in mineral content. In addition to fluoride-based systems, CPP-ACP, and calcium glycerophosphate are agents used to remineralize MIH lesion structures (29, 105). Topical applications of 10% CPP-ACP, CPP-ACFP, calcium glycerophosphate, 5% NaF varnish, and 5% NaF varnish with tricalcium phosphate were more effective for severe lesions (91, 93, 97, 101-103, 106). In contrast, minimal improvement was observed in mild lesions. Fluoride toothpaste (1450 ppm) alone worsened the lesions over time (97, 101). This may relate to the higher mineral needs of severely affected enamel, which CPP-ACP, with its calcium and phosphate contents, may

better address than fluoride alone. While both CPP-ACP and fluoride show benefits, CPP-ACP appears more suited for severe lesions.

9.1.2. Remineralization outcome measures

Five main diagnostic test systems are used for diagnosing early caries lesions: fluorescence, visual or visual-tactile classification systems, radiographic imaging, transillumination and optical coherence tomography, and electrical conductance or impedance technologies (107-109). A recent systematic review observed similar outcomes with wide prediction intervals, indicating uncertainty in diagnostic accuracy for each tool (109). To evaluate the effect of CPP-ACP on improving WSLs, our major limitation was that studies only used three evaluation systems to measure remineralization: Fluorescence-based methods (LF, QLF) and visual change scores.

In our MIH study, only fluorescence-based tools, such as LF and QLF, were included (108, 110, 111). There are other accurate quantitative in vitro methods to measure the mineral content of enamel in MIH, such as X-ray microtomography (XMT) (112-114). However, despite their quantitative precision, these methods are laboratory-based and are not applicable in daily clinical practice.

Laser Fluorescence

LF devices, such as DIAGNOdent, measure the fluorescence emitted from carious or hypomineralized enamel and relate it to lesion severity. These values should be interpreted with caution, as they provide indirect measurements of remineralization, such as the presence of bacterial porphyrins in carious lesions (86) or increased protein levels for non-carious hypomineralized enamel (115). In addition, factors such as moisture, plaque, and surface texture can affect readings (8, 116), and only low levels of bacterial metabolites (porphyrins) are present at early carious stages (117). DIAGNOdent has high sensitivity and low specificity for the detection of primary caries in permanent teeth (118, 119). These are indirect outcomes for remineralization, but despite their limitations, they are the currently clinically available methods.

One study has demonstrated a moderately strong correlation between LF scores and the mechanical properties of MIH-affected enamel (115). Still, there is a lack of robust evidence for the relationship between LF and MIH severity. Accurate measurement of

remineralization is challenging, as the reduction in LF or QLF readings observed during studies does not always correspond to a noticeable clinical improvement (63). Therefore, LF results should still be combined with visual inspection and consideration of the symptoms of patients (111, 116).

Quantified Light-Induced Fluorescence

QLF (Inspektor Research Systems, Amsterdam, The Netherlands) allows the quantification of mineral loss from enamel due to changes in fluorescence intensity (120). The Inspektor Pro™ (Inspektor Research Systems, Amsterdam, The Netherlands) system has an intra-oral fluorescence camera, illuminating the tooth surface with blue light from a xenon arc lamp and capturing green and red fluorescence. While green fluorescence is considered to be an indirect measure of enamel porosity and lesion severity, red fluorescence is used as an indicator of oral hygiene from matured biofilm (121). The QLF-D Biluminator™ (Inspektor Research Systems BV, Amsterdam, The Netherlands) uses a single-lens reflex camera with blue and white LED lights. The images of healthy tooth surfaces have a whitish appearance instead of green, while demineralized areas look darker (122). Through both systems, mineral loss in enamel is estimated by calculating the percentage fluorescence loss between carious enamel and adjacent healthy enamel, expressed as ΔF. This method is suggested as a more specific method than LF for detecting early signs of surface caries (123).

9.1.3. Remineralizing agents- CPP-ACP and Fluoride

Although CPP-ACP has been demonstrated to have anti-cariogenic activity *in vitro and in situ* (124-128), the results of in vivo experiments are still controversial and do not seem to show similar clinical efficacy as would be expected from in vitro data (72, 73, 76, 80).

There is conflicting evidence on the efficacy of CPP-ACP and fluoride on remineralization. While we found that the effect of CPP-ACP was not superior to that of fluoride alone in remineralizing early carious lesions, and no difference was found in LF values between the groups, despite their relevant action, Ma, Lin (49) demonstrated that CPP-ACP was effective in repairing the enamel *in vitro*. In contrast, *in vivo*, CPP ACP plus fluoride was as effective as fluoride alone. However, the in vitro conditions do not

replicate the variable effects of acid exposure, dental plaque, salivary fluid, bicarbonate and proteins, and fluoride exposure in vivo.

Tao, Zhu (129) found mixed results based on LF values; CPP-ACP plus fluoride was more effective than fluoride alone on the occlusal surfaces but not on the smooth surfaces of teeth. Only three studies were included, pooling together 3–24 week time-points. In contrast, we have included more studies at separate follow-up time points, showing the effectiveness of CPP-ACP. In QLF data, no difference in effect was observed between those groups. Wu, Geng (130) also showed a significant difference benefiting CPP-ACP plus fluoride over fluoride alone using LF values by DIAGNOdent. However, in the values of DMFS/dmfs index and enamel decalcification index (EDI), they did not find a significant improvement by CPP-ACP over fluoride alone. Sharda, Gupta (131) also tested other agents besides CPP-ACP using DIAGNOdent. They showed the superiority of CPP-ACP plus fluoride over fluoride alone but included only three studies. However, when investigating the caries preventive role of CPP-ACP, they found no significant difference between CPP-ACP and control, except when they pooled CPP-ACP and xylitol treatments together. Under those circumstances, they found a significant effect. However, it was not relevant to the assessment of CPP-ACP aloneÍ but rather to the small but significant effect of xylitol.

Limited evidence is available on the effect of CPP-ACP on MIH. In contrast, *in situ* studies have indicated increased mineral content and physical strength after the topical application of CPP-ACP in MIH-affected enamel (132) and demonstrated that CPP-ACP could accelerate and enhance the maturation of enamel structure in MIH (133). Kumar, Goyal (134) showed a reduction in the carbon content of hypomineralized enamel slabs and a consequent increase in Ca, P, and F after applying CPP-ACP and fluoride varnish. Despite the limited evidence on fluoride use for remineralization in MIH (93, 105, 134), topical FV is recommended to prevent caries in patients with MIH, along with regular dental checkups every 3-to-6 months and a healthy diet with controlled sugar intake (135, 136). In contrast, a longitudinal study demonstrated an increased risk of dental caries and susceptibility to enamel breakdown in molars affected by MIH, regardless of fluoride varnish application (137). In our study, the progression of lesions in teeth severely affected by MIH that used only fluoride toothpaste coincided with the increased

susceptibility to caries in severe MIH shown by previous studies—as severity increases, hypersensitivity occurs, and oral hygiene deteriorates (28, 138). Conflicting evidence on the efficacy of CPP-ACP and fluoride may arise from variations in study designs, sample characteristics, and even the severity of MIH lesions. Differences in formulations and application methods could also contribute, highlighting the need for standardized protocols.

9.1.4. Hypersensitivity Management

The evaluation of hypersensitivity in children is clinically challenging due to the subjective nature of their pain perception (25), which may be influenced by emotional, psychological, and environmental factors (28). Tactile, cold, and evaporative air stimuli are commonly used and recommended for the induction of dentinal pain, as they are physiological and reproducible (139). The Schiff Cold Air Sensitivity Scale (SCASS) is widely used to measure DH (140). Face scales, such as the Wong-Baker FACES Pain Rating Scale (WBFPRS), are visual tools for measuring pain intensity, particularly in children. These scales display facial expressions, ranging from no pain (neutral expression) to severe pain (distressed expression), and patients select the face that best reflects their pain (141, 142). In the present study, we used face scales (89, 92, 94-96, 98, 99) in addition to the SCASS. Although visual analog, numerical, verbal, and face pain scales and the SCASS are all accurate and recommended for assessing dentinal hypersensitivity, the SCASS demonstrated the highest sensitivity and specificity and should be considered the preferred scale (143). In addition, the SCASS has been effectively used in pediatric populations (26, 27). Compared to fluoride varnish, we have found that hypersensitivity is significantly reduced when using CPP-ACP products. Separate analyses of their mean effects showed this trend across various CPP-ACP combinations, with a more significant mean reduction than fluoride varnish.

MIH enamel is characterized by a hardened surface layer that forms over intact and degraded lesions, which may limit the deeper mineralization of apparently intact lesions (21). This may explain the seemingly more relevant effect of CPP-ACP on hypersensitivity than on remineralization, as released calcium and phosphate ions can precipitate into the open dentinal tubules and form a protective superficial layer of calcium phosphate that prevents external stimuli from reaching the nerves but not from

penetrating a deeper level for proper remineralization of the body of the lesion. Moreover, as previously discussed, fluorescence-based tools are indirect methods for monitoring remineralization, and studies have reported conflicting results on the effectiveness of laser fluorescence (LF) as a valuable method for detecting remineralization (144-147). Minor mineral changes may not be accurately detected by LF devices (145, 146, 148), and research suggests that these devices are less effective in assessing outer and inner enamel, showing a stronger correlation with lesion depth than with mineral loss (149). Therefore, these findings should be interpreted with caution.

Promising New Agents

Different agents are clinically used for remineralizing WSLs, such as bioactive glass (BAG) and self-assembling peptides. Salah, Afifi (150) investigated the efficacy of two BAG types compared to CPP-ACP, combining in-office and home applications for 1 month. Lesions in the Bio-BAG group reduced 65% in size at 6 months, while both N-BAG and CPP-ACP decreased WSLs by approximately 32%. Another RCT (151) compared the effect of fluoride varnish with tricalcium phosphate and self-assembling peptide. It showed a significant increase in remineralization of post-orthodontic WSLs in both groups in one-to-six-month time intervals, exhibiting better remineralizing capacity of self-assembling peptides compared to the effect of fluoride varnish. However, further well-controlled clinical trials are necessary to support the effectiveness of these promising materials in this respect.

Other materials, such as amine fluoride toothpaste, arginine and calcium carbonate paste, hydroxyapatite paste, low-level laser treatment, and silver diamine fluoride, have been initially explored for MIH. All of them exhibited a moderate effect on hypersensitivity, with low-level laser treatment showing the best results, followed by SDF, but only two studies could be included (41, 88). Previous studies have suggested that low-level laser therapy (LLLT) may help alleviate dentinal hypersensitivity (DH), although its effectiveness is debated (152-154), with some results potentially influenced by placebo effects (155). A recent review also found that silver diamine fluoride (SDF) at a concentration of 38% may reduce DH, but its long-term effects remain uninvestigated (156, 157). Furthermore, a recent in vitro study (158) observed an enhanced remineralization effect in artificial carious lesions when CaGP was combined with

conventional fluoride toothpaste. Similarly, an in situ study by Emerenciano, Delbem (159) reported that the incorporation of nano-sized β-CaGP into toothpaste significantly increased the bioavailability of calcium and phosphate, resulting in a higher remineralization effect compared to fluoride toothpaste (1100 ppm) alone. Despite promising results, further research on these agents is needed before recommending them.

9.2. Strengths

Both systematic reviews and meta-analyses adhered to a strict methodology according to the PRISMA guidelines. Study I was the most comprehensive and updated meta-analysis to examine the clinical efficacy of CPP-ACP versus fluoride alone on remineralization of WSLs. A previous meta-analysis (49) included primarily in vitro data, and only two clinical trials were considered. We could include multiple RCTs, which had not been considered in the previous meta-analyses. In contrast to other previous meta-analyses (129, 131), we performed statistical analyses at multiple time points (one, three, and 6 months) to estimate the effects over time.

Study II was the first complex quantitative analysis of available MIH strategies to manage remineralization and hypersensitivity. Only validated MIH diagnostic criteria (EAPD, Weerheijm, and Ghanim) were included, and many patients were included, particularly in hypersensitivity assessments. Conducting subgroup analyses according to MIH lesion severity could offer valuable insights for clinicians.

9.3. Limitations

Both Study I and Study II had several limitations. First, the low number of studies included in the pair-wise meta-analysis limits the interpretation of our findings. Standard random effects meta-analysis methods perform poorly when applied to a few studies only (160). Furthermore, due to the heterogeneity of control groups investigated, study II also used a single-arm meta-analysis to provide an overall estimate of treatment effect, which impacts the interpretation of the results. Promising interventions for MIH hypersensitivity, such as low-level laser, were underrepresented, limiting definitive conclusions on their efficacy, which affected the robustness of the recommendations. Furthermore, the available data might have insufficient power to estimate the between-study heterogeneity accurately (161).

In our first study, only RCTs were included - excluding observational studies; however, this may have introduced a potential inclusion bias. In contrast, Study II included both interventional and observational study designs, which, while providing a broader perspective, the limitations of observational studies, such as inadequate control for confounders, selection bias, and methodological variability in study conduct, may have introduced biases to the analysis.

Another limitation is the age heterogeneity between studies, especially in Study I. Besides the different physical properties of enamel and saliva pH between primary and permanent dentitions (162, 163), no clinical differences in the effect of CPP-ACP and fluoride on remineralization have been reported. Additionally, compliance with the treatment schedule, the quality of self-application, and self-reporting of pain may be affected by the patient's age. There was high heterogeneity in the treatments used; concentration, formulation, and application regimen also varied. Despite the protocol instructions, studies reported a lack of patient compliance and failed to follow-up product use at recall visits. The short follow-up period analyzed – 6 months maximum– prevented conclusions on interventions' long-term efficacy and durability. Furthermore, some subgrouping analyses based on MIH lesion severity/opacity color could not be performed for hypersensitivity.

However, the main limitation of the present work is the use of surrogate outcomes. We must acknowledge that fluorescence-based outcomes for remineralization, used by the included studies, are indirect measures that cannot show the microstructural features of teeth and the dynamic changes during the early stages of lesions. Therefore, the results should be interpreted with great caution. For hypersensitivity, different scales and measurement methods may have also affected the comparability of the results.

Finally, the high risk of bias reported in some studies and overall low certainty of the evidence further affects the confidence in the pooled results and limits the generalizability of these findings.

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10. CONCLUSIONS

10.1. Study I

The combination of CPP-ACP and fluoride is not significantly superior to fluoride alone in improving WSLs when assessed through laser fluorescence and visual area change. Additionally, topical fluoride could arrest or reverse the progression of early carious lesions, suggesting its effectiveness on WSLs. However, the certainty of evidence supporting these findings is very low. These results highlight the need for further high-quality studies and the development of more effective treatments than CPP-ACP in complementing fluoride and achieving substantial improvements in WSLs.

10.2. Study II

Although CPP-ACP did not demonstrate a significantly superior effect than fluoride in remineralizing MIH lesions through fluorescence-based methods, it is more effective than fluoride in reducing hypersensitivity. Other agents such as SDF, CaGP, and low-level laser demonstrated mild-to-moderate effects on remineralization and hypersensitivity, though the evidence remains inconclusive. These results are limited by heterogeneity, wide variability in treatment protocols, and short-term analysis. High-quality RCTs with longer follow-ups on the effectiveness of combination treatments and lesion severity are needed to strengthen the evidence and establish more precise clinical guidelines for managing MIH.

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11. IMPLEMENTATIONS FOR PRACTICE

Scientific results must be translated rapidly into clinical practice (164, 165). Therefore, our results indicate the limited benefit of combining CPP-ACP with fluoride over fluoride alone for remineralization in early carious lesions, reaffirming that daily fluoridated toothpaste remains a robust approach for early-stage caries management.

While several agents (fluoride varnish, CPP-ACP, CaGP, fluoride toothpaste) were tested, only CPP-ACP showed consistent effects, though the clinical significance remains limited. Therefore, CPP-ACP could be integrated into management plans alongside symptom management approaches, but further studies are needed to confirm long-term effectiveness and clinical relevance. Alternative agents, such as fluoride varnish and CaGP, could be considered adjunctive options, but their variable effects and uncertainties require careful clinical judgment.

CPP-ACP proved the most effective in managing hypersensitivity associated with MIH, especially for moderate to severe cases, and should be prioritized in treatment protocols. Low-level laser therapy (LLLT) emerges as a promising adjunctive option for addressing hypersensitivity.

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12. IMPLEMENTATIONS FOR RESEARCH

Future studies should include large-sample sizes with more extended follow-up periods and consistent methodologies to further comprehend the clinical efficacy of CPP-ACP in remineralizing early carious lesions. These studies should also focus on accurate outcomes, such as dentine caries. Besides this, substantially more effective products should be developed to achieve robust beneficial additional effects over fluoride.

Due to the limited and homogenous available data, transparent and standardized guidelines for managing remineralization and hypersensitivity MIH are not yet possible. Therefore, further robust randomized controlled trials should be performed for each agent with consistent control groups and standardized protocols to increase the certainty of the evidence. Studies need more uniform and longer follow-up times to better assess the long-term impact of non-invasive treatments. SCASS should be used for adequate dentin hypersensitivity assessment, and a description of lesion characteristics (dental group – incisors/molars, opacity color/severity) would allow for a more detailed comparison between interventions. Future studies should further explore novel therapies, such as low-level laser treatment and SDF, which were underrepresented in our study. The moderate quality of existing evidence calls for well-designed research to establish evidence-based clinical protocols to manage MIH effectively.

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13. IMPLEMENTATIONS FOR POLICYMAKERS

Policymakers should continue promoting fluoride use at an appropriate concentration and dose for the prevention and treatment of caries, as fluoride alone has demonstrated effectiveness in arresting or reversing early carious lesions despite the low certainty of evidence. Resources should focus on ensuring universal access to fluoridated toothpaste and community water fluoridation to support early-stage caries management, besides investments in oral hygiene education, especially for high-risk populations. The findings also suggest that the inclusion of CPP-ACP in clinical guidelines for remineralization may not be justified due to its limited additional benefit over fluoride alone. However, its effectiveness in reducing hypersensitivity in MIH cases justifies its integration into specific treatment protocols for managing moderate to severe symptoms.

Efforts should also address the development of novel and more effective remineralization agents that can complement fluoride and provide substantial clinical improvements. Investment in high-quality, standardized research is critical to reducing the variability in treatment protocols and outcomes observed in current evidence. Policymakers must enable large-scale, long-term, randomized controlled trials to establish reliable, evidence-based guidelines. Other promising therapies for MIH hypersensitivity, such as low-level laser treatment and SDF, require further exploration and potential integration into public health frameworks. Expanding access to these therapies can help reduce the psychosocial burden associated with MIH while controlling costs and improving quality of life.

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14. FUTURE PERSPECTIVES

Building on our current findings, we plan to advance research in managing early caries lesions and molar-incisor hypomineralization within our research group and contribute to developing novel biomimetic and diagnostic technologies that improve the clinical outcomes of remineralization strategies and facilitate their integration into routine dental care.

We intend to explore innovative approaches to remineralization that complement and enhance the action of fluoride, as well as in vivo diagnostic tools capable of real-time monitoring of demineralization and remineralization processes. We plan to conduct well-designed clinical studies and other evidence-based methodologies to address these priorities.

Therefore, we expect to contribute to establishing robust, standardized clinical protocols for managing early caries lesions and MIH and further significant advancements in the field while improving clinical outcomes and patient quality of life.

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