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Remineralization Agents in Orthodontics: Systematic Review

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Abstract

The objective of this systematic review was to comprehensively assess and review the long-term remineralizing potential of different remineralizing agents in white spot lesions those occurring after orthodontic treatment. A comprehensive search was performed in two electronic databases, PubMed and Cochrane. The search terms used were related to remineralization agents and orthodontics, utilizing Mesh (Medical Subject Headings) terminologies. The studies included in the review analyzed the effectiveness of remineralization agents in the context of orthodontics, up until December 2022. In selection procedure, 147 articles were extracted by electronic database search, and 27 duplicate articles were excluded. 89 articles were excluded after reading the whole text as they didn't meet the inclusion and exclusion criteria, so 31 articles were selected. The agents examined in the studies included fluoride-containing dentifrices, sodium fluoride gel, acidulated phosphate fluoride (APF) gel, toothpastes, varnishes, different formulations of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), Miswak sticks (chewing sticks made from Salvadora persica), sugar-free chewing gum, resin infiltration, Duraphat (fluoride varnish), sealant, self-administered and professionally administered fluoride gel, and micro abrasion , Self-assembling peptides , Bio-active glass. The review aimed to provide detailed insights into the efficacy of these agents in promoting remineralization and reversing white spot lesions which is helpful for clinician in their practice.

Keywords: Enamel demineralization; Enamel remineralization; White spot lesions; Orthodontics; Randomized controlled trial.

Full length review article **Dr .S Rahul Raj*, e-mail: rahulsureshkottakkal*@gmail.com*

1. Introduction

Maintaining good oral hygiene is crucial during orthodontic treatment. The appliances used in orthodontics have various attachments that are prone to plaque accumulation. This plaque buildup over a prolonged period can lead to demineralization around the brackets, resulting in the formation of white spot lesions. To prevent plaque accumulation, it is important to do good oral hygiene practices like regular brushing, usage of interdental brushes, use of mouthwashes, and ensure the proper removal of excess material around the brackets. By following these practices, the risk of white spot lesions can be reduced [1]. Orthodontic treatment often involves the use of fixed attachments on the tooth that can cause development of white spot lesions due to enamel demineralization. These lesions not only compromise the aesthetics of the dentition but also indicate an increased risk of cavities and enamel breakdown. Remineralizing agents have been widely explored as a preventive approach to mitigate enamel demineralization and promote remineralization during orthodontic treatment[2]However, a comprehensive evaluation of the efficacy and clinical applications of these agents is essential.

White spot lesions are precursors of dental caries that arise on the teeth as undesirable situations during fixed orthodontic appliance therapy. White spot lesions are defined as subsurface enamel porosities that arise due to carious demineralization. Typically, these lesions present as a milky opacity when located on a smooth tooth surface [2]. Dental caries is now recognized as a dynamic disease process in which a balance exists between demineralization and protective factors that promote remineralization. The process of caries lesion development becomes active when demineralization outweighs remineralization [3].This new understanding of caries has opened up opportunities for the remineralization of early-stage carious lesions, also known as White Spot Lesions. Remineralization is a natural repair process that occurs for non-cavitated lesions. It involves the rebuilding of a new surface on existing crystal remnants in subsurface lesions, which remain after demineralization. This process relies on the presence of calcium, phosphate ions, and fluoride, which assist in the remineralization process. When there are sufficient amounts of these ions present in the saliva or plaque, they can facilitate the remineralization of enamel that has been previously demineralized [4].

Demineralization is a process that occurs when plaque acids dissociate, releasing protons (H+) that dissolve the minerals in tooth enamel. When the pH drops below the critical level of 5.5 (lower than the normal pH range of 6.2 to 7.6), calcium and phosphate ions are lost from the enamel. This leads to the weakening of the enamel and the formation of chalky demineralized areas known as white spot lesions. If left untreated, these lesions can progress to the development of dental caries [2]. However, it is possible to arrest and even repair white spot lesions in their early stages without the need for invasive dental procedures. This can be achieved by promoting a net gain of minerals during the remineralization process. In modern dentistry, the focus is on effectively managing white spot lesions in a non-invasive manner to prevent disease progression and enhance oral aesthetics, strength, and function. Recent technologies have seen a surge of minimally invasive procedures for early diagnosis and reversal of white spot lesions. [4] By utilizing these non-operative techniques, it is possible to detect white spot lesions accurately and reliably at an early stage. This early detection enables dentists to diagnose such lesions promptly and implement appropriate preventive measures to promote remineralization and prevent further deterioration. The use of newer diagnostic aids plays a crucial role in facilitating early detection, allowing for timely intervention and treatment [5]. Topical fluorides are commonly used agents for the treatment of white spot lesions (WSLs). These include fluoride toothpastes, fluoride varnishes, and fluoride mouth rinses [1]. However, the effectiveness of these methods relies on patient compliance, which may vary and impact their efficacy. To address this issue, alternative topical fluoride delivery methods, such as the application of varnish and other remineralizing agents, have been developed. These methods provide better control over the delivery of fluoride and other remineralizing agents, reducing the reliance on patient compliance. By utilizing these alternative methods, the efficacy of treatment for WSLs can be improved, and the need for strict patient compliance can be minimized. In addition to the traditional topical fluorides, there are several newer methods of remineralization that can be used for the treatment of white spot lesions (WSLs). These include:

1.Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP): CPP-ACP is a bioactive complex that helps to stabilize calcium and phosphate ions in the oral environment, promoting remineralization. [1]

2.Usage of antimicrobial agents: Certain antimicrobial agents, such as chlorhexidine or essential oils, may be used in conjunction with remineralization therapies to control bacterial growth and enhance the effectiveness of treatment.(6)

3.Self assembling peptide: Anionic P114 is very effective in remineralization of white spot lesions [4]

4.Varnishes: Flouride varnishes have been effectively proven for white spot lesions treatment . [1]

5.Micro abrasion: Micro abrasion involves the removal of a thin layer of enamel using an abrasive agent, allowing for the penetration of remineralizing agents into the subsurface lesions [2].

6.Resin infiltration: Resin infiltration is a minimally invasive technique that involves filling the porous enamel with resin materials to improve the appearance and strength of the affected area [1].

7.Amorphous calcium phosphate (ACP): ACP is a bioactive material that can release calcium and phosphate ions, promoting remineralization. [1]

8.Bioactive glass: Bioactive glass is a material that can release ions, such as calcium and phosphate, to aid in remineralization and repair of WSLs [4].

9.Tricalcium phosphate (TCP) and ß-TCP: These calcium phosphate compounds have shown potential for promoting remineralization in WSLs [4]. These newer methods provide additional options for the management and treatment of WSLs, allowing for tailored approaches based on the specific needs and characteristics of each case. To accurately evaluate demineralization and remineralization processes, it is important to measure the amount of mineral lost or gained and identify the locations of these changes. Various techniques are available for direct and indirect quantification of minerals, including:

1.Microhardness: This method measures the resistance of the tooth surface to indentation and is commonly used to assess mineral changes [7].

2.Transverse Micro Radiography: This technique involves imaging thin tooth sections using X-rays to quantify mineral density changes [8].

3.Polarized light microscopy: By examining tooth sections under polarized light, mineralized areas can be visualized and assessed [8].

4.Scanning Electron Microscopy (SEM): SEM provides detailed information about surface topography, crystalline structure, and electrical behavior of the tooth specimen.[10]

5.Confocal Laser Scanning Microscopy: This method utilizes laser light to create high-resolution 3D images of mineralized tooth structures[11]

6.Microcomputed tomography (micro-CT): Micro-CT scan the tooth to create detailed 3D images, allowing for quantification of mineral changes[12].

7.Diagnodent pen: This handheld device uses laser fluorescence to detect and quantify mineral changes in tooth surfaces.[13]

8.Surface Microhardness: Similar to microhardness, this technique measures the resistance of the tooth surface to indentation but is specifically focused on surface mineral changes[7]

9.Conventional radiography: Traditional X-rays can provide information about mineral changes in the tooth structure[7]

10.Digital subtraction radiography: This method compares two digital X-ray images taken at different times to assess mineral density changes.[14]

11.Laser light methods: Techniques such as digital imaging, fiber-optic transillumination (DFOTI), and quantitative light-induced fluorescence use laser light to quantify mineral changes.[15]

12.Energy Dispersive Spectroscopy (EDS): EDS, coupled with SEM, analyzes the elemental composition of tooth surfaces to assess mineral content [16].

Among these techniques, surface microhardness is widely used due to its cost-effectiveness. SEM combined with EDS provides valuable information on surface characteristics and mineral content. The choice of technique depends on the specific research or clinical needs and the level of detail required for analysis. The susceptibility of individuals undergoing orthodontic treatment to white spot lesions necessitates the evaluation of the effectiveness of various remineralizing agents in reversing these lesions. This knowledge is crucial for orthodontists to ensure the smooth and effective continuation of treatment. The objective of this systematic review was to comprehensively assess and review the long-term remineralizing potential of different remineralizing agents in both naturally occurring white spot lesions and those occurring after orthodontic treatment. The review aimed to provide detailed insights into the efficacy of these agents in promoting remineralization and reversing white spot lesions which is helpful for clinician in their practice.

2. Materials and methods

Search strategy:

A comprehensive search was performed in two electronic databases, PubMed and Cochrane, using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) standards as the basis for article selection. The search terms used were related to remineralization agents and orthodontics, utilizing Mesh (Medical Subject Headings) terminologies. The search items were combined using Boolean operators (OR, AND) to refine the search results. The studies included in the review analyzed the effectiveness of remineralization agents in the context of orthodontics, up until December 2022.

PICOS question*:* In this evaluation, we will assess the efficiency and security of remineralizing substances employed for the prevention and treatment of WSLs (white spot lesions) in individuals undergoing fixed orthodontic treatment in various orthodontic environments.

PICOS ANALYSIS:

Population: Participants eligible for this study include individuals of any gender, age, residing in any city or country, and belonging to any ethnicity or socio-economic status. They should either have at least one white spot lesion on the outer surface of their teeth caused by fixed orthodontic treatment or are scheduled to undergo such treatment and will be monitored for the development of white spot lesions, with no specific limitations imposed.

Intervention: Rejuvenating agents employed to address pre-existing white spot lesions caused by orthodontic treatment or to prevent the formation of orthodontically induced white spot lesions will be investigated. Various forms or active ingredients of remineralizing materials will be treated as distinct interventions.

Comparison: Any other kind of remineralised agents or control/placebo.

Outcome: The study will assess the incidences of white spot lesions (WSLs), as well as the severity of lesions measured by metrics such as the WSL index, enamel decalcification index, DIAGNOdent pen reading, quantitative light-induced fluorescence, and other relevant indicators. Additionally, adverse events related to the interventions will be monitored, and various other outcomes related to WSLs will be evaluated.

Study design: systematic review, meta-analysis , randomized controlled trials (RCT's) , prospective cohort , retrospective studies with control group.

Inclusion criteria

1.**Study Design**: Only include studies that meet the criteria of systematic reviews, meta-analyses, randomized controlled trials (RCTs), controlled clinical trials, prospective cohort studies, or retrospective studies with a control group. Exclude case reports, opinion articles, letters, and editorials.

2.Participants: Include studies involving orthodontic patients of any age and gender who have developed white spot lesions during or after orthodontic treatment.

3.Intervention: Include studies evaluating any interventions or management approaches for white spot lesions in orthodontics, such as remineralization agents, fluoride varnishes, toothpaste, micro abrasion, resin infiltration, or others.

4.Comparison: Include studies with a control group or comparative interventions, where applicable.

5.Outcome Measures: Include studies reporting relevant outcomes related to the management of white spot lesions, such as lesion regression, improvement in lesion appearance, reduction in demineralization, patient satisfaction, or others.

6.Language: Include studies published in English.

Exclusion criteria:

1.Irrelevant Studies*:* Exclude studies that are not directly related to the management of white spot lesions in orthodontics.

2.Animal or in vitro Studies: Exclude studies conducted on animals or in laboratory settings unless they provide crucial insights not available from human studies.

3.Insufficient Data: Exclude studies with insufficient data or incomplete reporting of outcomes that cannot be obtained after contacting the authors or through other means.

4.Publication Type: Exclude conference abstracts, posters, and unpublished studies, as they may not undergo the same rigorous peer-review process as published articles.

5.Duplicate Studies: Exclude duplicate studies or multiple publications from the same study to avoid counting the same data multiple times.

The search was carried out by three independent observers according to CONSORT guidelines using Mesh terms in the following search databases – PubMed, Cochrane. After reviewing the title, abstract, and materials and methods, the studies which met the inclusion criteria were extracted. The selection procedure is illustrated by the flow diagram, 147 articles were extracted by electronic database search, and 27 duplicate articles were excluded. 89 articles were excluded after reading the whole text as they didn't meet the inclusion and exclusion criteria, so 31 articles were selected at the end of selection process Table 1 represents the Preferred reporting items for systematic reviews and meta-analyses (prisma) using flow chart.

3. Results and Discussions

Quality assessment

Each study was assessed using the evaluation method described in the Cochrane Handbook for Systematic Reviews (Version 5.1.0 [updated March 2011] Julian PT Higgins and Sally Green 2011). The quality assessment of the included trials was undertaken independently by three reviewers. The evaluated domains included the randomization method, allocation concealment, assessor-blinding, dropouts, and risk of bias. Each domain was categorized as having either a low, high, or unclear risk of bias. Consequently, the overall risk level for each study was classified as follows: "Low Risk" (if it received a "Yes" in all four main categories), "Moderate Risk" (if two out of four categories did not receive a "Yes"), "Low Risk" (if all four categories were deemed adequate), or "Unclear" (if there was an unclear risk of bias in one or more domains).

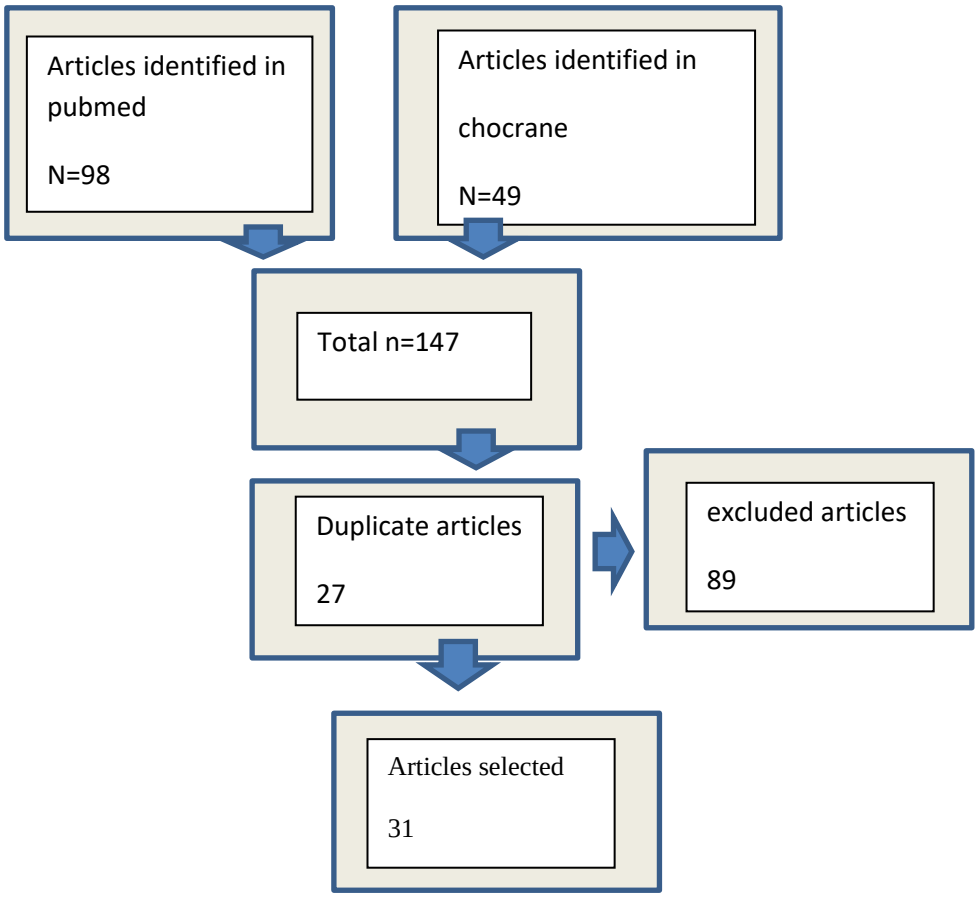
Result

The articles obtained through PRISMA have been summarized in Table 2. Thirty-two studies that met the inclusion criteria were summarized into tabular form based on risk of bias, sample justification, study type, allocation concealment, assessor blinding, dropout description, baseline comparison, method of error, inclusion and exclusion criteria also was assessed and reported in the Table 3.

Discussion

This systematic review aims to evaluate and summarize the long-term remineralizing potential of various remineralizing agents in both naturally occurring white spot lesions and those that develop after orthodontic treatment. The objective is to provide comprehensive insights into the efficacy of these agents in promoting remineralization and reversing white spot lesions, thereby assisting clinicians in their practice. The focus of all the studies included in this review was to evaluate the effectiveness of remineralizing agents in orthodontics in reversal of white spot lesions occurring during and after orthodontic treatment. Various remineralizing agents and techniques encompassed in this review include fluoride-containing dentifrices, sodium fluoride gel, acidulated phosphate fluoride (APF) gel, toothpastes, varnishes, different formulations of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), Miswak sticks (chewing sticks made from Salvadora persica) and sugar-free chewing gums , resin infiltration techniques , Duraphat (fluoride varnish), sealant administration , self-administered and professionally administered fluoride gel, and microabrasion etc . A study conducted by Mehmet Akin et al [18] (2012) evaluvated and compared the effectiveness of CPP-ACP and fluoride rinse and microabrasion in treating white spot lesions .This study in concluded that the use of CPP-ACP was very effective in post orthodontic remineralization and microabrasion was effective in cosmetic improvement in long standing white spot lesions . Another study by YUXIAN WANG et al [45] (2017)and Beerens MW[29] (2010) et al also concluded that CPP-ACP was effective in the regression of white spot lesions. Louis soloman [49]. (2022)et al found that resin infiltration techniques and CPP-ACP have durable esthetic improvement in terms of reduction in area and color of post orthodontic white spot lesions. A study conducted by Chung HK et al [19] (2019) compared the effectiveness of fluoride agents like clinpro 5000, clinpro crème and MI paste and concluded that clinpro 5000 has a better effect. A study conducted by F Eren Giray [32]et al (2018) showed that both resin infiltration and fluoride varnish are clinically feasible and effective in treating anterior white spot lesions (WSLs). Resin infiltration, specifically, can inhibit the progression of caries and should be considered as a viable alternative to fluoride treatment for managing WSLs. Vanessa Salvadego De Queiroz [23](2015) and Hosam A Baeshen [20]. (2012) et al found the effectiveness of fluoride dentrifices and fluoridated miswaks on reduction of white spot lesions when used on a regular basis. Rania salah et al [52] (2003) compared the effectiveness of bioactive glass (45S5) and casein-phosphopeptide stabilized-amorphous calcium phosphate (CPP-ACP) and concluded that Bio-BAG showed a significant lesion size percent reduction compared to CPP-ACP.

TABLE 1: PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA) FLOW CHART.



RESULT: The articles obtained through PRISMA have been summarized in the table 2.

TABLE 2: SUMMARIES OF THE STUDIES INCLUDED:

Sr.no	year	author	Type of study	intervention	Number of participants	Conclusion
1	1987	M. M. O'Rellly [17]	invivo	1.dentrifice (1,100 ppm fluoride as sodium fluoride). 2.sodium fluoride (0.05% sodium fluoride.) 3.apf gel (1.23% APF gel)	20	The results of this study allow the recommendation of an improved caries preventive regimen for the orthodontic patient in the form of daily home use of [1] a fluoride dentifrice coupled with (2) a low-concentration (0.05% sodium flouride) commercially available fluoride mouthrinse.
2	2016	Sombir Singh,[5]	a clinical trial	1.toothpaste(1000ppm fluoride toothpaste colgate total) 2.varnish(5%NAF flouritop SR) 3.cpp-acp(GC tooth moose)	45	The application of fluoride varnish and CPP-ACP, along with the twice-daily use of fluoride toothpaste, did not yield any extra advantages in the process of remineralizing white spot lesions that occur after orthodontic treatment.
3	2012	Mehmet Akin [18]	invivo	Control- toothpaste Group 2 – sodium fluoride rinse (0.025%NAF colgate plax) Group 3- cpp-acp(GC tooth moose) Group 4- microabrasion +GC toothmoose	80	Utilizing CPP-ACP may offer greater benefits compared to using fluoride rinse for the remineralization of white spot lesions that develop after orthodontic treatment. Additionally, microabrasion proves to be an effective approach for enhancing the cosmetic appearance of persistent white spot lesions.
4	2019	Chung H. Kau [19]	Randomized trial	Clinpro 5000(1.1%NAF +5000ppm F), Clinpro Tooth Crème(0.21%NAF+950 ppm F), and MI-Paste Plus(0.2%NAF)	100	The application of Clinpro 5000, Clinpro Cream, and MI Paste Plus all demonstrates a reduction in the development of white spot lesions, with notably improved outcomes compared to prior study findings. Notably, Clinpro 5000 exhibits a slightly more favorable effect than the other two test pastes.
5	2011	Hosam A. Baeshen, [20]	invivo	Miswak 19 (0.5 NAF containing miswak) 18 (non fluoridated miswak)	37	Regular use of fluoridated miswaks has shown to promote the remineralization of white spot lesions (WSLs). Additionally, the DIAGNOdent pen could prove to be a valuable instrument for diagnosing and tracking alterations in WSLs over a relatively brief time frame.
6	2016	Mehmet Bayram [21],	invivo	casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)(GC tooth moose) fluoride varnish (bifluoride 12)	15	Saliva, as well as saliva combined with remineralizing agents such as fluoride varnish and CPP-ACP, led to an augmentation in the microhardness and surface roughness values of stripped enamel surfaces, which had initially experienced a decrease due to the stripping process.
7	2010	Ann Bröchner[22]	invivo	10% casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) (GC tooth moose) Flouride tooth paste (colgate 1100ppm F)	60	The application of a casein phosphopeptide-stabilized amorphous calcium phosphate agent as a topical treatment for white spot lesions following the removal of orthodontic appliances led to a notable reduction in ΔF values and a decrease in the lesion area.
8	2015	Vanessa Salvadego De Queiroz[23]	invivo	fluoride dentifrice	35	Results indicate the patients used fluoride dentrifice had significant less whitespot lesions using using optical microscopy and fluorescent laser (DIAGNOdent)
9	1999	C J Klebe[24]	invivo	Enamelon(fluoride dentrifice)	27 lesions (group 1) 41 lesions group 2	Brushing with a remineralizing toothpaste resulted in a significant reduction in the size of newly formed orthodontic white spots within a span of 2 months.
10	2007	Anita Andersson[25]	invivo	casein phosphoprotein-amorphous calcium phosphate (CPP-ACP) topacal , fluoride mouthwash (0.005%NAF)	26	Both groups showed a substantial enhancement in clinical white spot lesion (WSL) scores over time. However, there was a statistically significant distinction ($p < 0.01$) between the two groups regarding the number of sites that completely disappeared after 12 months, favoring the CPP-ACP regimen with 63%, compared to 25% in the other group.
11	1998	Susan AI-Khateeb[26]	invivo	fluoride dentifrice.	7	The findings of this study highlight the effectiveness of the QLF method in longitudinally

						tracking minor alterations in early-stage enamel lesions. As a result, this method holds great promise for evaluating the impact of preventive and therapeutic interventions in different groups at risk of dental caries, including orthodontic patients.
12	1995	A. Gray[27]	invivo	Sugar free low tack chewing gum	25 (study group) 25 (non ortho dontic control group	Employing low-tack chewing gum in combination with reinforcing oral hygiene practices should, therefore, play a role in lowering the occurrence of white spot lesions among orthodontic patients who are receiving fixed appliance treatment.
13	2009	D.L. Bailey[28]	invivo	Cpp Acp Fluoride mouth rinses (tooth moose 10%w/v) Fluoride toothpaste(1000 ppm naf)	45	The outcomes of this latest clinical trial demonstrate that a remineralizing cream containing CPP-ACP led to a noteworthy improvement in the regression of white spot lesions when compared to an identical cream that does not contain CPP-ACP.
14	2010	Beerens MW[29]	invivo	Cpp-Afcp (MI paste plus) Fluoride free control paste + calcium Sodium fluoride 0.2%w/v 900 ppm	54	In both study groups, minimal alterations in fluorescence loss were observed 12 weeks after orthodontic appliance removal. However, a gradual reduction in the presence of aciduric bacteria and Streptococcus mutans in the dental plaque was noted over the course of the study.
15	1994	BjQrn ~gaard[30]	invivo	nonfluoridated toothpaste	7	short-term lesions induced in pumiced vital teeth regress speedily in vivo with a halfvalue time of about a week.
16	1991	L. Mitchell[31]	invivo	Fluoride releasing bonding material	24	Although bond failiure rate was increased there were less occurance of white spot lesions
17	2018	F Eren Giray[32]	Randomized clinical trial	Resin infiltration(ICON DMG) Fluoride (5%NAF) varnish (clinpro white varnish)	23	Resin infiltration and fluoride varnish have been shown to be both clinically viable and effective approaches for managing anterior white spot lesions (WSLs). The use of resin infiltration to impede the advancement of dental caries should now be regarded as a credible alternative to traditional fluoride treatments.
18	2015	Tao He[33]	Randomized invivo	The fluoride varnish (Duraphat 5%NAF) Fluoride toothpaste(1000ppm F)	240	The clinical feasibility and efficacy of both resin infiltration and fluoride varnish in addressing anterior white spot lesions (WSLs) have been demonstrated. Employing resin infiltration to halt the progression of dental caries should now be considered a viable alternative to conventional fluoride treatments.
19	2022	Lauren N. Flynn[34]	Randomized clinical trial	MI Varnish and ProSeal sealant	40	With regular reapplication, both MI Varnish and ProSeal sealant offer comparable levels of protection throughout the course of orthodontic treatment.
20	2004	Dr.R.wilmot[35]	randomized clinical controlled trial.	low fluoride mouthrinse/toothpaste (50ppm NAF)	21 (26 participants 5 dropout)	White demineralized lesions that occurred after orthodontic treatment diminished in size by about 50% within the 6 months following the treatment. This study found no clinical benefit in using the low fluoride mouthwash and toothpaste in the research.
21	2016	Niko C. Bock1[36]	Randomized clinical trial	Professional fluoride/placebo gel application Self administere fluoride gel administration(1.25%NAF Gel)	39	According to the findings of this study, there was no discernible difference in the occurrence of white spot lesions (WSL) when post-orthodontic high-dose fluoride treatment was considered.
22	2010	Michael A. Robertson[37]	Randomized clinical trial	MI Paste Plus (GC America, Alsip, Ill), Cpp-Afcp	60	MI Paste Plus proved to be effective in preventing the formation of new white spot lesions during orthodontic treatment and also reduced the number of existing white spot lesions.
23	2017	Moniek W. Beerens1[38]	Randomized clinical traial	CPP-ACP + sodium fluoride (MPP 35 ml, Recaldent; GC Benelux Europe, Leuven, Belgium)] fluoride-free control paste + calcium	51	The supplementary application of MPP (presumably MI Paste Plus) in individuals with subsurface enamel lesions following orthodontic fixed appliance treatment did not lead to any improvement in these lesions during the year following the removal of orthodontic appliances.
24	2012	OTA ´ VIO JOSE´ PRAXEDES-NETO.[48]	invivo	Floridated tooth paste	30 patients	The utilization of fluoridated toothpaste did not yield any additional positive effects.
25	2017	Andrew P. Garry.[46]	Randomized controlled clinical trial	fluoride toothpaste CPP-ACP paste (Tooth Mousse)	12 patients	Remineralization took place irrespective of the treatment group assignment. Nonetheless, the inclusion of Tooth Mousse™ led to a notably heightened remineralization effect compared to fluoride alone. Tooth Mousse™ could prove

						advantageous for orthodontic patients at a high risk of demineralization.
26	2019	Robert S. D. Smyth [47]	Randomized controlled trial	1.1%NAF +5000ppm F), Clinpro Tooth Crème(0.21%NAF+950 ppm F), and MI-Paste Plus(0.2%NAF)	120	The application of Clinpro 5000, Clinpro Tooth Crème, and MI Paste Plus all results in a reduction in white spot lesions, as compared to previous studies. Notably, Clinpro 5000 was found to have a slightly more favorable effect compared to the other two test pastes.
27	2022	Louis Solaman Simon[49]	Randomized controlled trial	Cpp acp(GC tooth moose) Resin infiltration(ICON DMG)	60	Both resin infiltration and CPP-ACP have been effective in achieving aesthetically pleasing and long-lasting improvements by reducing the area and color of white spot lesions that occur after orthodontic treatment.
28	2016	Farzin Heravi [51]	Clinial trail	casein phosphopeptide-amorphous calcium phosphate and fluoride (MI Paste Plus) hydroxyapatite and fluoride (Remin Pro) fluoridated toothpaste (crest 1000ppm NAF)	39	Both MI Paste Plus and Remin Pro were found to be effective in decreasing the area, enhancing mineral content, and improving the appearance of demineralized enamel. This suggests that these products are suitable recommendations for managing white spot lesions that occur after orthodontic treatment.
29	2003	rania salah [52]	randomized controlled trial	bioactive glass (45S5)(novamin slurry and toothpaste) compared to casein-phosphopeptide stabilized-amorphous calcium phosphate (CPP-ACP)(recaldent paste)	60	The Bio-BAG group exhibited a highly significant reduction in lesion size percentage when compared to the control group.
30	2021	Mennatallah Atef Aboulnaga [53]	randomized controlled trial	Remin Pro Forte (hydroxyapatite, fluoride, xylitol, ginger, curcuma-containing cream)vs Remin Pro (hydroxyapatite and fluoride, xylitol)	20	Both Remin Pro Forte and Remin Pro have demonstrated success in diminishing caries, increasing mineral content, and improving the appearance of demineralized enamel. These findings indicate that both products can be recommended for managing white spot lesions that occur after orthodontic treatment.
31	2017	Said KARABEKİROĞLU[54]	Clinical study	fluoride-containing toothpaste. (1,450 ppm ; Colgate Total) CPPACP((Tooth Mousse, GC Asia,) paste	41 patients	The daily application of CPP-ACP paste did not yield superior results compared to standard care in terms of enhancing the appearance of white spot lesions (WSLs) after a 36-month period.

Table 3: Thirty-one studies that met the inclusion criteria were summarized into tabular form based on risk of bias, sample justification, study type, allocation concealment, assessor blinding, dropout description, baseline comparison, method of error, inclusion and exclusion criteria also was assessed and reported in the table 3

Sl.no	Study	Study Type	Randomization	Allocation concealment	Assessor blinded	Dropouts described	Risk of bias	Sample justified	Baseline comparison	I/E criteria	Method of error
1	M. M. O'Rellly [17] (1987)	Invivo	no	no	no	no	Low	No	no	no	no
2	Sombir singh [5](2011)	Invivo	yes	yes	yes	no	Low	no	no	no	no
3	Mehmet Akin [18](2012)	Invivo	no	no	no	no	Low	yes	yes	yes	No
4	Chung H kau [19](2019)	Invivo	yes	no	no	no	Low	no	no	no	no
5	HosamA Baeshen [20](2011)	Invivo	yes	no	yes	no	Low	yes	yes	yes	yes
6	Mehmet bayram [21](2016)	Invivo	yes	no	no	no	Low	no	no	yes	no
7	Ann brochner [22] (2010)	Invivo	yes	yes	yes	yes	Low	yes	yes	yes	yes
8	Vanessa Salvadego De Queiroz [23] (2015)	Invivo	no	no	no	no	Low	yes	yes	yes	no
9	C J Klebe[24](1999)	Invivo	no	no	no	no	Low	no	yes	yes	no
10	Anita Andersson [25](2007)	Invivo	yes	no	no	no	High	yes	no	yes	no
11	Susan AI-Khateeb[26](1998)	Invivo	no	no	no	no	Low	yes	yes	no	no
12	A. Gray [27](1995)	Invivo	yes	no	yes	yes	Low	yes	no	yes	no
13	D.L. Bailey [28](2009)	Invivo	yes	no	yes	no	Low	yes	no	yes	no
14	Beerens MW [29](2010)	Invivo	yes	no	yes	no	Low	yes	yes	yes	no
15	BjQrn ~gaard, [30](1994)	Invivo	no	no	no	no	low	no	no	yes	No
16	L. Mitchell [31](1991)	Invivo	no	no	no	no	Low	no	no	yes	no
17	F Eren Giray [32](2018)	Randomized control trial	yes	no	no	no	Low	no	yes	no	no
18	Tao He [33](2015)	Randomized control trial	yes	yes	yes	no	High	yes	yes	yes	no
19	Lauren N. Flynn[34] (2022)	Randomized control trial	yes	no	no	no	Low	no	yes	yes	no
20	Dr.R.wilmot [35](2004)	Randomized control trial	yes	no	no	yes	Low	yes	no	yes	yes
21	Niko C. Bock,[36](2016)	Randomized control trial	yes	no	yes	yes	Low	no	no	yes	no
22	Michael A[37].(2010)	Randomized control trial	yes	no	no	no	Low	yes	yes	yes	no
23	Moniek W. Beerens[38],(2017)	Randomized control trial	yes	no	no	no	Low	no	yes	yes	no
24	OTA ´ VIO JOSE´ PRAXEDES-NETO.[48] (2012)	Invivo	no	no	no	no	High	yes	yes	yes	no
25	Andrew P. Garry.[46] (2017)	Randomized controlled clinical trial	yes	no	no	no	Low	yes	yes	no	no
26	Robert S. D. Smyth .[47] (2019)	Randomized controlled clinical trial	yes	no	yes	no	High	yes	yes	no	no
27	Louis Solaman Simon .[47] (2022)	Randomized controlled trial	yes	yes	yes	yes	Low	yes	yes	yes	no
28	Farzin Heravi .[51] (2016)	Clinical trial	no	no	no	yes	Low	yes	yes	yes	no
29	rania salah.[52] (2003)	randomized controlled trial	yes	no	yes	no	Low	yes	yes	yes	no
30	Mennatallah Atef Aboulnaga.[53] (2021)	randomized controlled trial	yes	no	no	no	Low	no	no	yes	no
31	Said KARABEKİROĞLU1.[54] (2017)	Clinical study	no	no	no	no	Low	no	yes	yes	no

A study conducted by A. Gray et al [27] (1995) suggested that incorporating low-tack chewing gum, along with reinforcing oral hygiene practices, can contribute to a decrease in the occurrence of white spot lesions among orthodontic patients receiving treatment with fixed appliances. A study conducted by Rasiga et al [56] concluded that Aloe Vera gel showed promising results by significantly remineralising WSLs. Flaxseed paste and fluoride toothpaste had SMH recovery which was lesser than Aloe Vera gel but, these two groups significantly improved the colour of WSL. This review critically analyses existing literature and examines the effectiveness of different remineralizing agents, their application methods, and the outcomes observed in clinical studies. The findings of this review will significantly contribute to the current knowledge base on the management of white spot lesions, aiding clinicians in making informed decisions regarding treatment options.

4. Conclusions

This systematic review presents a comprehensive assessment of the efficacy and clinical applications of remineralizing agents in orthodontics. The agents examined in the studies included fluoride-containing dentifrices, sodium fluoride gel, acidulated phosphate fluoride (APF) gel, toothpastes, varnishes, different formulations of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), Miswak sticks (chewing sticks made from Salvadora persica), sugar-free chewing gum, resin infiltration, Duraphat (fluoride varnish), sealant, self-administered and professionally administered fluoride gel, and microabrasion. The review aimed to assess the efficacy and outcomes associated with these diverse approaches and formulations of remineralization agents. The results indicated that when it comes to remineralizing white spot lesions, bioactive glass and CPP-ACP are superior to other methods. Bioactive glass demonstrates greater potential for remineralization and significantly reduces lesion size more than CPP-ACP. The findings from this review can assist orthodontists in making evidence-based decisions regarding the selection and application of remineralizing agents to prevent and treat white spot lesions during orthodontic treatment. Further research is necessary to establish standardized protocols, optimize treatment regimens, and enhance the understanding of the long-term effects of remineralizing agents in orthodontic practice.

References

[1] H. Hu, C. Feng, Z. Jiang, L. Wang, S. Shrestha, X. Su, Y. Shu, L. Ge, W. Lai, F. Hua, H. Long. (2019). Effectiveness of remineralising agents in prevention and treatment of orthodontically induced white spot lesions: a protocol for a systematic review incorporating network meta-analysis. Systematic Reviews. 8. 339. 10.1186/s13643-019-1253-8.

[2] I. Gavrilovic. (2014) White Spot Lesions in Orthodontic Patients: Formation, Prevention and Treatment. J Oral Hyg Health 2:154.

[3] J. D. Featherstone. (2008). Dental caries: a dynamic disease process. Australian dental journal, 53(3), 286–291.

[4] N. Preethi. (2014). Remineralizing Agent -Then and Now -An Update. Dentistry. 04. 10.4172/2161-1122.1000256.

[5] S. Singh, P. Goyal, A. Utreja, A. K. Jena. (2016). Effects of various remineralizing agents on the outcome of post-orthodontic white spot lesions (WSLs): a clinical trial. Progress in orthodontics, 17(1), 25

[6] S. S. Temel, B. Kaya (2019) Diagnosis, Prevention and Treatment of White Spot Lesions Related to Orthodontics. Int J Oral Dent Health 5:085

[7] J. Mandava, Y. S Reddy, S. Kantheti, U. Chalasani, R. C. Ravi, R. Borugadda, , R. K. Konagala, (2017). Microhardness and Penetration of Artificial White Spot Lesions Treated with Resin or Colloidal Silica Infiltration. Journal of clinical and diagnostic research : JCDR, 11(4), ZC142–ZC146.

[8] Y. Koshimitsu, Yusuke, M. Sayed, A. Saad, J. Tagami G. Inoue, M. Ikeda. (2020). Transverse Micro Radiography Analysis of the Effect of Experimental Calcium-Containing Primer System on Demineralized Enamel.Crystals. 10. 1087. 10.3390/cryst10121087

[9] R. Rajan, R. Krishnan, B. Bhaskaran, S. Kumar. (2015). A Polarized Light Microscopic Study to Comparatively evaluate Four Remineralizing Agents on Enamel viz CPP-ACPF, ReminPro, SHY-NM and Colgate Strong Teeth 1. IJCPD. 8. 42-47. 10.5005/jp-journals-10005-1281.

[10] R. Talaei, Z. Hoseini, R. Ghorbani, N. Ameli. (2019). Mineral Content Identification of White Spot Lesions Around Orthodontic Brackets Following the Use of Different Concentrations of Nano-Hydroxyapatite Mouthwash And Fluoride Gel. Middle East Journal of Rehabilitation and Health Studies. In Press. 10.5812/mejrh.96516.

[11] W. Li, J. Huang, X. Chen, R. Shi, L. Jiang, Y. Zhao. (2011). Qualitative analysis of re mineralized carious lesions subjected to fluoride supplement through confocal laser scanning microscope. Open Journal of Stomatology.01. 55-60. 10.4236/ojst.2011.13010

[12] E. Sadyrin ,M. Swain , B. Mitrin, I. Rzhepakovsky, A. Nikolaev, V. Irkha, , D. Yogina, N. Lyanguzov ,S. Maksyukov, S. Aizikovich. (2020). Characterization of Enamel and Dentine about a White Spot Lesion: Mechanical Properties, Mineral Density, Microstructure and Molecular Composition. Nanomaterials (Basel, Switzerland), 10(9), 1889

[13] N. Gupta, M. Sandhu, V. Sachdev, P. Jhingan. (2019). Comparison of Visual Examination and Magnification with DIAGNOdent for Detection of Smooth Surface Initial Carious Lesion-Dry and Wet Conditions. International journal of clinical pediatric dentistry, 12(1), 37–41

[14] S. Valizadeh, S. Ehsani, F. Esmaeili, M. A. Tavakoli. (2008). Accuracy of digital subtraction radiography in combination with a contrast media in assessment of proximal caries depth. Journal of dental research, dental clinics, dental prospects, 2(3), 77–81.

[15] M. Khoroushi, M. Kachuie. (2017). Prevention and Treatment of White Spot Lesions in Orthodontic Patients. Contemporary clinical dentistry, 8(1), 11–19.

[16] Z. A. Shaik, T. Rambabu, G. Sajjan, M. Varma, K. Satish, V. B. Raju, S. Ganguru, N. Ventrapati. (2017).QuantitativeAnalysis of Remineralization of Artificial Carious Lesions with Commercially Available Newer Remineralizing Agents Using SEM-EDX- In Vitro Study". Journal of clinical and diagnostic research : JCDR, 11(4), ZC20–ZC23.

[17] M. O'Reilly, J. D. Featherstone, (1987). Demineralization and remineralization around orthodontic appliances: an in vivo study. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 92(1), 33–40.

[18] M. Akin, F. A. Basciftci. (2012). Can white spot lesions be treated effectively?. The Angle orthodontist, 82(5), 770–775.

[19] C. H. Kau, J. Wang, A. Palombini, N. Abou-Kheir, T. Christou. (2019). Effect of fluoride dentifrices on white spot lesions during orthodontic treatment: A randomized trial. The Angle orthodontist, 89(3), 365–371.

[20] H. A. Baeshen, P. Lingström, D. Birkhed (2011). Effect of fluoridated chewing sticks (Miswaks) on white spot lesions in postorthodontic patients. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 140(3), 291–297.

[21] M. Bayram, A. Kusgoz, C. Yesilyurt, M. Nur. (2017). Effects of casein phosphopeptide-amorphous calcium phosphate application after interproximal stripping on enamel surface: An in-vivo study. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 151(1), 167–173.

[22] A. Bröchner, C. Christensen, B. Kristensen, S. Tranæus, L. Karlsson, L. Sonnesen, S. Twetman. (2011). Treatment of post-orthodontic white spot lesions with casein phosphopeptide-stabilised amorphous calcium phosphate. Clinical oral investigations, 15(3), 369–373.

[23] V.S. De Queiroz, P.R. Nouer, C.P. Tabchoury, Y.B. Lima-Arsati, D.F. Nouer, (2015). In vivo evaluation of fluoride dentifrice and diet control on the demineralization/remineralization process using laser readouts at the margin of the orthodontic bracket/enamel interface. American journal of dentistry, 28(1), 23–27.

[24] C.J. Kleber, J.L. Milleman, K.R. Davidson, M. S. Putt, C.W. Triol, A. E. & Winston. (1999). Treatment of orthodontic white spot lesions with a remineralizing dentifrice applied by toothbrushing or mouth trays. The Journal of clinical dentistry, 10(1 Spec No), 44–49.

[25] A. Andersson, K. Sköld-Larsson, A. Hallgren, L. G. Petersson, S. Twetman, (2007). Effect of a dental cream containing amorphous cream phosphate complexes on white spot lesion regression assessed by laser fluorescence. Oral health & preventive dentistry, 5(3), 229–233.

[26] S. Al-Khateeb, C. M. Forsberg,, E. J. Josselin, B. Angmar-Månsson. (1998). A longitudinal laser fluorescence study of white spot lesions in orthodontic patients. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 113(6), 595–602.

[27] A. M. Gray, M. M. Ferguson. (1996). The use of low-tack chewing gum for individuals wearing orthodontic appliances. Australian dental journal, 41(6), 373–376.

[28] D. L. Baile, G. G. Adams, C. E. Tsao, A. Hyslop, K. Escobar, D. J Manton, E. C. Reynolds, & M. V. Morgan (2009). Regression of post-orthodontic lesions by a remineralizing cream. Journal of dental research, 88(12), 1148–1153.

[29] M. W. Beerens, M. H. van der Veen, H. van Beek, J. M. ten Cate, (2010). Effects of casein phosphopeptide amorphous calcium fluoride phosphate paste on white spot lesions and dental plaque after orthodontic treatment: a 3-month follow-up. European journal of oral sciences, 118(6), 610–617.

[30] B. Ogaard, J. J. Ten Bosch (1994). Regression of white spot enamel lesions. A new optical method for quantitative longitudinal evaluation in vivo. American journal of orthodontics and dentofacial orthopedics: official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 106(3), 238–242.

[31] L. Mitchell (1992). An investigation into the effect of a fluoride releasing adhesive on the prevalence of enamel surface changes associated with directly bonded orthodontic attachments. British journal of orthodontics, 19(3), 207–214.

[32] F. E Giray, M. A. Durhan, E. Haznedaroglu, B. Durmus, I. O. Kalyoncu, I. Tanboga (2018). Resin infiltration technique and fluoride varnish on white spot lesions in children: Preliminary findings of a randomized clinical trial. Nigerian journal of clinical practice, 21(12), 1564–1569.

[33] T. He, X. Li, Y. Dong, N. Zhang, Y. Zhong, W. Yin, D. Hu. (2016). Comparative assessment of fluoride varnish and fluoride film for remineralization of postorthodontic white spot lesions in adolescents and adults over a 6-month period: A single-center, randomized controlled clinical trial. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 149(6), 810–819.

[34] L.N. Flynn., K. Julien., A. Noureldin., & P.H. Buschang. (2022). The efficacy of fluoride varnish vs a filled resin sealant for preventing white spot

lesions during orthodontic treatment. The Angle orthodontist, 92(2), 204–212.

[35] D. Willmot. (2004). Scientific section: White lesions after orthodontic treatment: Does low fluoride make a difference?. Journal of orthodontics. 31. 235-42; discussion 202. 10.1179/146531204225022443.

[36] N. C. Bock, L. Seibold, C. Heumann, E. Gnandt, M. Röder, S. Ruf (2017). Changes in white spot lesions following post-orthodontic weekly application of 1.25 per cent fluoride gel over 6 months-a randomized placebo-controlled clinical trial. Part I: photographic data evaluation. European journal of orthodontics, 39(2), 134–143.

[37] M. A. Robertson, C. H. Kau, J. D. English, R. P. Lee, J. Powers, J. T. Nguyen. (2011). MI Paste Plus to prevent demineralization in orthodontic patients: a prospective randomized controlled trial. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 140(5), 660–668.

[38] M. W. Beerens, , J. M. Ten Cate, M. J. Buijs, M. H. van der Veen (2018). Long-term remineralizing effect of MI Paste Plus on regression of early caries after orthodontic fixed appliance treatment: a 12-month follow-up randomized controlled trial. European journal of orthodontics, 40(5), 457–464.

[39] N. C. Bock, L. Seibold, C. Heumann, E. Gnandt, M. Röder, S. Ruf. (2017). Changes in white spot lesions following post-orthodontic weekly application of 1.25 per cent fluoride gel over 6 months-a randomized placebo-controlled clinical trial. Part II: clinical data evaluation. European journal of orthodontics, 39(2), 144–152.

[40] K. Indrapriyadharshini, P. D. Madan Kumar, K. Sharma, K. Iyer. (2018). Remineralizing potential of CPP-ACP in white spot lesions - A systematic review. Indian journal of dental research : official publication of Indian Society for Dental Research, 29(4), 487–496.

[41] D. Höchli, M. Hersberger-Zurfluh, S. N. Papageorgiou, T. Eliades, (2017). Interventions for orthodontically induced white spot lesions: a systematic review and meta-analysis. European journal of orthodontics, 39(2), 122–133.

[42] M. Sonesson, F. Bergstrand, S. Gizani, S. Twetman (2017). Management of post-orthodontic white spot lesions: an updated systematic review. European journal of orthodontics, 39(2), 116–121.

[43] H. Chen, X. Liu, J. Dai, Z. Jiang, T. Guo, Y. Ding. (2013). Effect of remineralizing agents on white spot lesions after orthodontic treatment: a systematic review. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics, 143(3), 376–382.e3.

[44] H. Hu, C. Feng, Z. Jiang, L. Wang, S. Shrestha, J. Yan, Y. Shu, L. Ge, W. Lai, F. Hua, H. Long. (2020). Effectiveness of remineralizing agents in the prevention and reversal of orthodontically induced white spot lesions: a systematic review and network meta-analysis. Clinical oral investigations, 24(12), 4153–4167.

[45] Y. Wang, F. Hua, H. Jiang. (2020). CPP-ACP May be effective, but not Significantly Greater than using Fluorides Alone, in Preventing and Treating white Spot Lesions Around Orthodontic Brackets. The journal of evidence-based dental practice, 20(1), 101416.

[46] A. P. Garry, N. L. Flannigan, L. Cooper, G. Komarov, G. Burnside, S. M. Higham. (2017). A randomised controlled trial to investigate the remineralising potential of Tooth Mousse™ in orthodontic patients. Journal of orthodontics, 44(3), 147–156.

[47] R. S. D. Smyth, J. H. Noar. (2019). Preventing white spot lesions with fluoride pastes. Evidence-based dentistry, 20(3), 88–89.

[48] O. J. Praxedes-Neto , B. C. Borges, C. Florêncio-Filho, A. C. Farias, J. Drennan, K. C. De Lima, (2012). In vivo remineralization of acid-etched enamel in non-brushing areas as influenced by fluoridated orthodontic adhesive and toothpaste. Microscopy research and technique, 75(7), 910–916

[49] L. S. Simon, J. K. Dash, S. Philip, S. Sarangi. (2022). Management of Post Orthodontic White Spot Lesions Using Resin Infiltration and CPP-ACP Materials- A Clinical Study. The Journal of clinical pediatric dentistry, 46(1), 70–74.

[50] R. A. A. E. G. Gohar, S. H. Ibrahim, O. M. Safwat, (2023). Evaluation of the remineralizing effect of biomimetic self-assembling peptides in post-orthodontic white spot lesions compared to fluoride-based delivery systems: randomized controlled trial. Clinical oral investigations, 27(2), 613–624

[51] F. Heravi, F. Ahrari, B. Tanbakuchi. (2018). Effectiveness of MI Paste Plus and Remin Pro on remineralization and color improvement of postorthodontic white spot lesions. Dental research journal, 15(2), 95–103.

[52] R. R. Salah, Afifi, H. A. Kehela, N. M. Aly, M. Rashwan, R. G. Hill. (2022). Efficacy of novel bioactive glass in the treatment of enamel white spot lesions: a randomized controlled trial. The journal of evidence-based dental practice, 22(4), 101725.

[53] M. A. Aboulnaga, M. M. Akah, O. E. Hassanein. (2022). Evaluation of Remineralization Potential of Remin Pro Forte vs Remin Pro on White Spot Lesions: A Randomized Clinical Trial. The journal of contemporary dental practice, 23(5), 520–526.

[54] S. Karabekiroğlu, N. Ünlü, E. Küçükyilmaz, S. Şener, M. S. Botsali, S. Malkoç. (2017). Treatment of post-orthodontic white spot lesions with CPP-ACP paste: A three year follow up study. Dental materials journal, 36(6), 791–797.

[55] https://clinicaltrials.gov/show/NCT04827966, 2021 | added to CENTRAL: 30 April 2021 | 2021 Issue 04

[56] R. Gandhi, D. Srinivasan, S. Duraisamy, R. Kannan. (2022). Comparison of the Remineralisation Potential between Flaxseed Paste, Aloe Vera Gel and Fluoride Toothpaste on Artificially Created White Spot Lesions around Orthodontic Brackets: An In-vitro Study. Journal of clinical and diagnostic research.