Journal of Orthodontic and Periodontal Biomaterials Research

2025, Volume 5, Issue 2, Page No: 92-104

Available online at: https://galaxypub.co/

Galaxy Publication

Preventive Strategies for White Spot Lesions Associated with Fixed Orthodontic Appliances: A Review

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Received: 02 August 2025; **Revised:** 28 November 2025; **Accepted:** 28 November 2025

ABSTRACT

This study provides a comprehensive review of scientific evidence addressing preventive measures for white spot lesions (WSLs) that develop as a consequence of fixed orthodontic treatment. WSLs, which arise from enamel demineralization, create both aesthetic and functional complications. The review focuses on assessing the efficacy of various preventive approaches aimed at minimizing WSL occurrence during orthodontic therapy. A detailed literature search was performed using MeSH terms including “white spot,” “fixed orthodontic treatment,” “CPP-ACP,” “topical fluoride,” and “demineralized lesion,” combined with the Boolean operator ‘AND’. Databases such as PubMed, EMBASE, Scopus, and OpenGrey were searched for studies published between January 2014 and September 2024. Inclusion criteria encompassed studies evaluating preventive strategies for reducing WSL risk in patients treated with fixed orthodontic appliances. Out of 41 retrieved studies, 17 met the selection criteria based on methodological quality and relevance. Multiple preventive modalities were identified as effective in mitigating WSL formation. Topical fluoride, especially in high-concentration varnish form, showed significant efficacy, with several studies reporting superior results compared to alternative treatments. Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) and its fluoride-enriched variant (CPP-ACPF) promoted enamel remineralization, particularly when used alongside fluoride toothpaste. Additionally, high-fluoride toothpaste and acidulated phosphate fluoride mouthwash reduced lesion incidence, reinforcing the role of consistent oral hygiene compliance. Periodic professional applications of fluoride varnish further improved preventive outcomes. The prevention of WSLs is essential for maintaining both the aesthetic and clinical success of orthodontic therapy. Combining fluoride-based treatments with CPP-derived compounds provides substantial protective benefits. Nonetheless, patient awareness and adherence to prescribed oral hygiene measures are fundamental. Continued research should aim to assess the long-term comparative efficacy of existing interventions and develop innovative approaches for WSL prevention.

Keywords: Preventive strategies, White spot lesions, Enamel demineralization, Fixed orthodontic treatment

How to Cite This Article: Kaczmarek LF, Jankowski TI, Wojcik A, Kowalski M, Kowalski MY, Svoboda PQ. Preventive Strategies for White Spot Lesions Associated with Fixed Orthodontic Appliances: A Review. J Orthod Periodontal Biomater Res. 2025;5(2):92-104. https://doi.org/10.51847/rx4OORuy8b

Introduction

Dental caries is a chronic and multifactorial infectious disease driven by bacterial activity, affecting a large proportion of the global population, particularly children and adults. It occurs when cariogenic microorganisms within dental plaque metabolize dietary sugars, producing acids that demineralize tooth enamel and eventually form cavities. The development of caries is influenced by several factors, including sugar intake, poor oral hygiene habits, and host-related conditions [1]. White spot lesions (WSLs) represent the earliest visible stage of caries,

characterized by subsurface enamel demineralization that produces an opaque, chalky appearance without cavitation. While remineralization can restore early lesions, prolonged demineralization leads to irreversible decay. Maintaining a balance between mineral loss and replacement is essential; however, even after remineralization, aesthetic defects may persist [2].

WSLs are particularly prevalent in orthodontic patients, often emerging within weeks of appliance placement, especially around brackets and beneath molar bands. Fixed orthodontic appliances complicate daily oral hygiene by promoting plaque retention, thereby increasing the likelihood of demineralization, which can compromise both aesthetic results and treatment success [3]. Brackets, as integral components of fixed orthodontic systems, significantly contribute to this problem due to their intricate design, which limits effective cleaning and creates additional surfaces for bacterial adhesion [4]. Materials with rougher surfaces and higher surface free energy further facilitate biofilm accumulation by enhancing bacterial attachment and protecting microbial colonies from shear forces. Additionally, bracket size and shape affect biofilm formation—smaller and simpler designs are generally preferred to minimize bacterial adherence and plaque accumulation [5].

Hence, patient education is fundamental before and during orthodontic treatment, emphasizing the importance of achieving optimal oral hygiene and understanding the limitations imposed by fixed appliances [6]. Individuals with orthodontic devices face a higher risk of developing WSLs and enamel demineralization, requiring preventive measures such as fluoride applications and remineralizing agents. These lesions frequently appear on the upper lateral incisors and canines adjacent to the brackets, typically within the first month of treatment, while cavity formation usually develops over several months [7].

Major risk factors for caries include high sugar consumption, inadequate brushing, insufficient fluoride exposure, and irregular dental visits, with children and adolescents being the most vulnerable. Socioeconomic and demographic variables—such as income, education, occupation, age, gender, and ethnicity—also play a role in caries susceptibility. Regular use of fluoride toothpaste and routine dental checkups remain key preventive practices [8]. Fixed orthodontic appliances not only increase plaque accumulation but may also cause discomfort, leading to aesthetic complications due to WSLs that appear during long-term treatment [9].

Fluoride-based prevention strategies include systemic supplementation, water fluoridation, and fluoride-containing dentifrices. The recommended fluoride concentration in drinking water is approximately 1 ppm, which offers protection against caries while minimizing the risk of fluorosis. In patients with enamel defects such as molar incisor hypomineralization (MIH), amelogenesis imperfecta, or fluorosis, fixed appliances may be contraindicated because of weak enamel bonding, structural fragility, and heightened plaque accumulation due to surface porosity [10].

Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) serves as a remineralizing agent by releasing bioavailable calcium and phosphate ions that penetrate demineralized enamel, promoting mineral deposition and inhibiting further acid-induced damage. Widely incorporated into oral care formulations, CPP-ACP enhances enamel repair and fortifies tooth structure against demineralization [11]. Fluoride, on the other hand, facilitates remineralization by substituting hydroxide ions in hydroxyapatite crystals with fluoride ions, forming fluorapatite—a compound with superior acid resistance that reinforces enamel and prevents decay [12].

The primary objective of this study is to analyze and synthesize current scientific literature evaluating the effectiveness of various preventive approaches in minimizing the development of white spot lesions among patients undergoing fixed orthodontic treatment.

Materials and Methods

A comprehensive literature review was undertaken to identify and analyze studies evaluating the efficacy of various preventive agents and interventions designed to minimize the occurrence of white spot lesions (WSLs) associated with fixed orthodontic treatment. The review process was conducted collaboratively by two independent reviewers (RGP and FSL), who assessed publications based on specific inclusion and exclusion criteria.

Inclusion criteria encompassed clinical case studies, randomized controlled trials, and systematic reviews that investigated WSL prevention among individuals undergoing fixed orthodontic therapy. Exclusion criteria included (1) studies addressing the treatment of WSLs after orthodontic therapy, (2) studies on WSL management unrelated to orthodontic treatment, (3) in vitro experiments, (4) animal studies, and (5) narrative reviews, systematic reviews, or meta-analyses.

The literature search employed both Medical Subject Headings (MeSH) and non-MeSH terms to ensure comprehensive coverage. The MeSH terms used were "Dental Caries," "Orthodontic Appliances," "Tooth Demineralization," "Fluorides," and "Caseins." Additional keywords, including "White Spot Lesions," "Fixed Orthodontic Treatment," "CPP-ACP," and "Topical Fluoride," were incorporated to capture studies not formally indexed under MeSH. Searches were conducted across multiple electronic databases—PubMed, EMBASE, Scopus, and OpenGrey—for publications dated between January 2014 and September 2024 (Appendix A). The initial screening was performed on June 16, 2024, followed by the article selection process, which took place between June and September 2024.

All retrieved records were initially screened by title and abstract, yielding 41 potentially relevant studies. After full-text evaluation, 17 articles met the inclusion criteria and were incorporated into this review. These selected studies comprised reviews, systematic reviews, in vitro and in vivo investigations, and randomized clinical trials **(Figure 1)**.

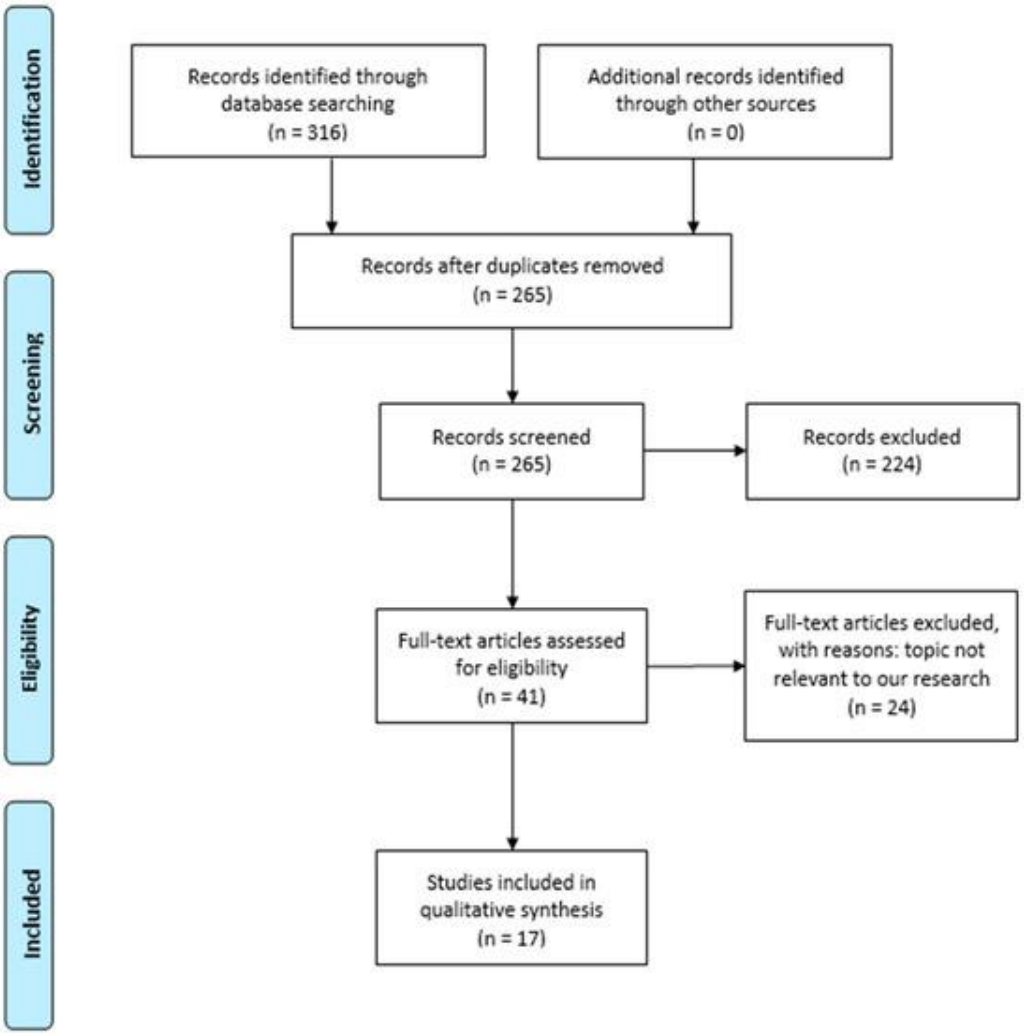

Figure 1. PRISMA 2009 flow diagram

Results and Discussion

From the database search, a total of 41 articles were initially identified as potentially relevant. After a detailed evaluation of the full texts and application of the inclusion and exclusion criteria, 17 studies were ultimately selected for analysis. These encompassed randomized controlled trials, systematic reviews, meta-analyses, as well as in vivo and in vitro investigations. The following table presents an organized and concise overview of the included studies drawn from the international scientific literature. Structured in columns, it outlines the title of each study selected according to the established criteria, along with the author, publication year, research

objective, methodology, and main conclusions. The selected works comprise a variety of study designs, including reviews, systematic reviews, laboratory-based (in vitro) and animal (in vivo) studies, and randomized clinical trials **(Table 1)**.

Table 1. Overview of Studies on Preventing and Managing White Spot Lesions (WSLs) in Fixed Orthodontic Treatment

Title and Reference	Authors and Date	Objective	Materials and Methods	Conclusions
Prevention and Treatment of White Spot Lesions During and After Treatment with Fixed Orthodontic Appliances: a Systematic Literature Review [13]	Lopatiene K, Borisovaite M, Lapenaite E (2016)	Explore evidence for WSL prevention using fluoride and casein products.	Analyzed controlled studies (2008–2016) on orthodontic patients with fixed appliances, sourced from PubMed, ScienceDirect, Embase, and Cochrane Library.	Fluoride and casein products reduce WSLs; CPP-ACP may prevent demineralization more effectively than fluoride rinses.
Fluorides for preventing early tooth decay (demineralised lesions) during fixed brace treatment [14]	Benson PE, Parkin N, Dyer F, Millett DT, Germain P (2019)	Determine if topical fluoride lowers new WSL incidence in orthodontic patients.	Reviewed randomized trials comparing fluoride products to placebo or no treatment, using Cochrane Library, Medline, and Embase.	High-fluoride toothpaste (5000 ppm) and professional fluoride foam (12,300 ppm) significantly lower WSL occurrence.
Prevention of white spot lesions with fluoride varnish during orthodontic treatment with fixed appliances: a systematic review [15]	Sonesson M, Twetman S (2023)	Assess fluoride varnish's impact on WSL prevention in orthodontic care.	Evaluated randomized trials (up to 2022) with fluoride varnish applied at least every three months.	Consistent fluoride varnish use effectively prevents WSLs in orthodontic patients.
Caries prevention during orthodontic treatment: In vivo assessment of high-fluoride varnish to prevent white spot lesions [16]	Perrini F, Lombardo L, Arreghini A, Medori S, Siciliani G (2016)	Investigate fluoride varnish's role in reducing WSLs in fixed appliance patients.	Conducted a split-mouth study with 24 patients, comparing varnished and non-varnished teeth for demineralization.	Fluoride varnish provides limited WSL protection, not significant with excellent oral hygiene.
Fluoride varnish for the prevention of white spot lesions during orthodontic treatment with fixed appliances: a randomized controlled trial [17]	Sonesson M, Brechter A, Abdulraheem S, Lindman R, Twetman S (2020)	Test ammonium fluoride varnish's ability to prevent WSLs.	Randomized 166 patients to fluoride varnish or placebo, applied every six weeks near brackets.	Ammonium fluoride varnish significantly decreases severe WSLs during treatment.
An Extensive Comparison of the Clinical Efficiency of Acidulated Phosphate Fluoride (APF) and Neutral Sodium Fluoride (NaF) Oral Rinses in the Prevention of White Spot Lesions during Fixed Orthodontic Treatment: A Randomized Controlled Trial [18]	Pilli LN, Singaraju GS, Nettam V, Keerthipati T, Mandava P, Marya A (2022)	Compare weekly NaF and daily APF mouthwashes for WSL prevention.	Randomized 90 patients into two groups for a six-month study.	Daily APF mouthwash is superior to weekly NaF for WSL prevention.

Systematic review of preventive and treatment measures regarding orthodontically induced white spot lesions [19]	Yazarloo S, Arab S, Mirhashemi AH, Gholamrezayi E (2023)	Evaluate evidence-based WSL prevention and treatment strategies.	Reviewed randomized trials (2015–2020).	Fluoride toothpaste is key; 5% fluoride varnish is advised for patients with suboptimal oral hygiene.
Effectiveness of self-applied topical fluorides against enamel white spot lesions from multi-bracketed fixed orthodontic treatment: a systematic review [20]	Sardana D, Manchanda S, Ekambaram M, Yang Y, McGrath CP, Yiu CKY (2019)	Examine self-applied fluorides for WSL prevention and repair.	Analyzed randomized trials from Cochrane Library, Embase, Medline, and Scopus.	Self-applied fluorides offer moderate WSL prevention, with weak evidence for repair.
Efficacy of CPP-ACP and CPP-ACPF for Prevention and Remineralization of White Spot Lesions in Orthodontic Patients: a Systematic Review of Randomized Controlled Clinical Trials [21]	Imani MM, Safaei M, Afnaniesfandabad A, Moradpoor H, Sadeghi M, Golshah A, Sharifi R, Mozaffari HR (2019)	Assess CPP-ACP and CPP-ACPF for WSL prevention and enamel repair.	Reviewed trials from Web of Science, Scopus, PubMed, and Cochrane Library.	CPP-ACP and CPP-ACPF effectively lower WSL rates and support enamel remineralization.
Effectiveness of amine fluoride mouthwash in preventing white spot lesions during fixed orthodontic therapy—A randomized control trial [22]	Ravi Kiran KR, Sabrish S, Mathew S, Shivamurthy PG, Sagarkar R (2023)	Evaluate amine fluoride mouthwash for WSL prevention.	Randomized 50 patients, using intraoral photographs to assess WSLs.	Amine fluoride mouthwash significantly outperforms fluoride toothpaste alone in reducing WSLs.
Preventive Effect of Professional Fluoride Supplements on Enamel Demineralization in Patients Undergoing Fixed Orthodontic Treatment: A Systematic Review and Meta-Analysis [23]	Babadi Oregani E, Jafari A, Masoud Sajedi S, Reza Motamedian S (2022)	Analyze professional fluoride methods for WSL prevention.	Reviewed RCTs from PubMed and Cochrane Library on varnishes, gels, and mouthwashes.	Regular fluoride varnish or daily mouthwash significantly reduces WSLs.
MI Varnish and MI Paste Plus in a caries prevention and remineralization study: a randomized controlled trial [24]	Rechmann P, Bekmezian S, Rechmann BMT, Chaffee BW, Featherstone JDB (2018)	Evaluate MI Paste Plus and MI Varnish for WSL prevention and repair.	Randomized 40 patients to experimental (fluoride toothpaste, MI Paste Plus, MI Varnish) or control groups for 12 months.	Experimental group had higher salivary fluoride, but WSL scores showed no significant difference.
Effectiveness of high-fluoride toothpaste on enamel demineralization during orthodontic treatment-a multicenter randomized controlled trial [25]	Sonesson M, Twetman S, Bondemark L (2014)	Test high-fluoride toothpaste's ability to prevent WSLs.	Randomized 424 adolescents to use 5000 ppm or 1450 ppm fluoride toothpaste.	High-fluoride toothpaste (5000 ppm) significantly reduces WSLs.
Evaluation of the Efficacy of Various Topical Fluorides on Enamel Demineralization	Reddy R, Manne R, Sekhar GC, Gupta S, Shivaram N, Nandalur KR (2019)	Compare topical fluorides for preventing demineralization near brackets.	Tested 100 premolars in vitro with fluoride varnish, APF gel, and toothpaste.	Fluoride varnish is most effective, followed by toothpaste, APF gel, and mouthwash.

Adjacent to Orthodontic Brackets: An In Vitro Study [26]				
White Spots: Prevention in Orthodontics-Systematic Review of the Literature [27]	Patano A, Malcangi G, Sardano R, Mastrodonato A, Garofoli G, Mancini A, Inchingolo AD, Di Venere D, Inchingolo F, Dipalma G, Inchingolo AM (2023)	Identify strategies to prevent WSLs during orthodontic treatment.	Reviewed studies (2018–2023) on orthodontic patients.	Fluoride toothpaste is essential; periodic professional fluoride gels and varnishes are recommended.
Effect of fluoride dentifrices on white spot lesions during orthodontic treatment: A randomized trial [28]	Kau CH, Wang J, Palombini A, Abou-Kheir N, Christou T (2019)	Compare Clinpro 5000, Clinpro Tooth Crème, and MI Paste Plus for WSL reduction.	Randomized three groups to use products for four months.	Clinpro 5000 slightly outperforms Clinpro Tooth Crème and MI Paste Plus in reducing WSLs.
Prevention of white spot lesions using three remineralizing agents: An in vitro comparative study [29]	Tahmasbi S, Mousavi S, Behroozibakhsh M, Badiee M (2024)	Compare NaF, CPP-ACPF, and Remin Pro for demineralization prevention.	Applied remineralizing agents daily to 56 premolars under pH cycling.	NaF is more effective than CPP-ACPF and Remin Pro in preventing WSLs.

In 2016, Lopatiene *et al.* conducted a systematic review to update the evidence on preventing white spot lesions (WSLs) in patients undergoing fixed orthodontic treatment, focusing on the use of fluoride-containing products and/or casein phosphopeptide-amorphous calcium phosphate (CPP-ACP). The review incorporated twelve studies, including clinical trials, cohort studies, and case reports. While four studies reported no notable improvement with fluoride applications such as varnishes or toothpaste, another four demonstrated significant benefits from fluoride-based interventions. CPP-ACP was observed to outperform fluoride rinses in post-treatment enamel remineralization. Overall, nine of the twelve studies concluded that using fluoride and/or CPP-ACP is effective in reducing or preventing WSLs [13].

Benson *et al.* evaluated the impact of topical fluoride in orthodontic patients for WSL prevention. Their results highlighted fluoride varnish as the most effective option, lowering the occurrence of new lesions to 11.7%, compared to 29.7% in the placebo group. Varnishes with lower fluoride concentrations were less effective, and fluoride gels applied quarterly showed no significant benefit. Professional fluoride foams applied every two months helped reduce lesion formation, emphasizing that consistent applications are crucial. High-fluoride toothpaste (5000 ppm) offered partial protection, with formulations containing amine or stannous fluoride outperforming standard sodium fluoride. The study underscored that both the concentration and frequency of fluoride applications are critical for optimal prevention [14].

Sonesson *et al.* investigated the preventive effect of periodic fluoride varnish use during orthodontic treatment. Seven randomized clinical trials, each lasting at least twelve months, were reviewed, in which varnishes were applied around brackets at intervals of three months or less. The products tested included 5% sodium fluoride, 5% sodium fluoride combined with CPP-ACP, difluorosilane, and 1.5% ammonium fluoride. Application frequency ranged from four-weekly to three-monthly, with study durations spanning 12 to 26 months. Findings consistently showed that regular fluoride varnish use reduced WSL formation, with additional benefits when fluoride was combined with CPP-ACP. The data highlighted the importance of application frequency in achieving preventive effectiveness [15].

The 2016 study by Perrini *et al.* assessed the in vivo effectiveness of Duraphat fluoride varnish in preventing WSLs using a split-mouth design with 24 participants. Varnish was applied to quadrants 1 and 3, leaving quadrants 2 and 4 untreated as controls. Participants received varnish either every three months (Group 1) or every six months (Group 2), with 5% sodium fluoride applied around brackets, alongside standard oral hygiene instructions. Results indicated a trend toward greater demineralization in untreated teeth, but no statistically significant differences were observed over 3, 6, 9, and 12 months. Treated incisors at nine months showed reduced demineralization, but overall differences across the groups were limited, and increasing application frequency did not markedly improve outcomes [16].

In 2020, Sonesson *et al.* tested a new fluoride varnish containing 1.5% ammonium fluoride for WSL prevention in adolescents with fixed orthodontic appliances. Participants were treated for at least twelve months and received either the test varnish or a placebo varnish every six weeks during check-ups, after plaque removal. The placebo was identical in appearance and handling but lacked ammonium fluoride. After application, patients avoided food or drink for one hour and brushed with 1450 ppm fluoride toothpaste. At the end of treatment, mild WSL prevalence was similar between groups, but the test varnish group had fewer severe lesions at the time of appliance removal [17].

In 2022, Pilli and colleagues investigated how two types of fluoride mouthwashes—neutral sodium fluoride (NaF) and acidulated phosphate fluoride (APF)—influence the development of white spot lesions (WSLs) following orthodontic treatment. Ninety patients were randomly split into two groups: one rinsed weekly with 0.2% NaF, and the other used 0.044% APF daily, each for one minute after brushing. Evaluations were conducted at 4, 12, and 24 weeks. Results showed that the NaF group experienced a steady rise in enamel demineralization scores, whereas the APF group initially worsened but improved by the final assessment. Statistically meaningful changes were seen across nearly all intervals for NaF, except between weeks 12 and 24, while APF only showed significant improvement between weeks 12 and 24 [18].

A 2023 review by Yazarloo *et al.* synthesized evidence from 23 studies, including randomized controlled trials, to examine preventive and therapeutic methods for WSLs caused by fixed orthodontic appliances. Preventive approaches included CPP-ACP products, fluoride-containing varnishes, toothpastes, mouthwashes, adhesives, and sealants, while therapeutic strategies focused on remineralizing agents, fluoride varnishes, and chlorhexidine rinses [19].

Sardana *et al.* explored how patient-applied topical fluorides affect WSLs during conventional braces therapy. Only three randomized trials were included: two addressed prevention, and one examined post-treatment lesion reversal. At bracket removal, one study showed a 250 ppm fluoride mouth rinse reduced lesion numbers compared to placebo, and 5000 ppm sodium fluoride toothpaste proved more effective than 1450 ppm toothpaste [20].

In 2019, Imani *et al.* evaluated CPP-ACP and CPP-ACPF in preventing and remineralizing WSLs. The analysis included thirteen studies, four using CPP-ACP and nine using CPP-ACPF, with control groups such as placebo, standard fluoride toothpaste, fluoride varnish, or mouthwash. Follow-up periods ranged from 3 to 36 months. Three studies suggested CPP-ACP enhanced remineralization, while one found no advantage. For CPP-ACPF, four studies demonstrated clinical benefit, while five showed no significant difference compared to controls [21].

Ravi Kiran *et al.* assessed the effect of amine fluoride mouthwash during fixed orthodontic treatment over six months. Patients were divided into a control group (toothpaste only) and an experimental group (toothpaste plus 480 ppm amine fluoride mouthwash). Baseline lesion scores were similar, but after six months, the experimental group showed a reduction in WSLs, whereas the control group's lesions worsened, indicating the preventive value of amine fluoride mouthwash [22].

Finally, Babadi Oregani *et al.* reviewed seven studies on the preventive effects of fluoride compared with placebo. Some studies applied fluoride varnish multiple times during treatment, one applied it once at treatment onset, another used fluoride mouthwash, and one compared high- versus standard-fluoride toothpaste. Across most studies, fluoride interventions reduced lesion number or severity, though a single varnish application showed no measurable benefit [23].

In 2018, Rechmann and colleagues explored whether combining MI Paste Plus (MIPP) with MI Varnish (MIV) could prevent or reverse white spot lesions in patients undergoing orthodontic treatment. The trial included 40 participants randomly divided into experimental and control groups. Those in the experimental group received MI Varnish containing 10% CPP-ACP and 5% NaF every three months and applied MI Paste Plus (10 percent CPP-ACP, 0.2 percent NaF, 900 ppm fluoride) nightly. The control group used standard fluoride toothpaste (1100 ppm) alongside a 0.05% NaF mouth rinse. Enamel demineralization was monitored using the enamel demineralization index (EDI) at baseline, three, six, and twelve months. While the control group's EDI rose slightly from 37.7 to 41.3, the experimental group showed a minor decrease from 42.9 to 40.2, but differences between the groups were not statistically meaningful [24].

Sonesson *et al.* investigated the impact of high-fluoride toothpaste on the development of white spot lesions in adolescents treated with fixed orthodontic appliances for at least one year. Participants in the test group used a 5000 ppm fluoride toothpaste, whereas controls used a standard 1450 ppm fluoride toothpaste, following identical brushing routines. Standardized brushes and toothpaste were supplied at the outset and every three months. At the study's start, both groups were comparable, but by the end, fewer patients in the high-fluoride group exhibited

white spot lesions (18.1%) than in the control group (26.6%). New lesion formation was more common in controls, and most lesions in both groups were thin-margined, with severe lesions being rare (1.2% in the experimental group versus 2.3% in controls) [25].

In an in vitro investigation, Reddy *et al.* (2019) compared different fluoride interventions for protecting enamel around orthodontic brackets using 100 extracted premolars. Teeth were divided into five groups: fluoride varnish, acidulated phosphate fluoride (APF) gel, fluoride toothpaste, sodium fluoride mouthwash, and an untreated control. Specimens underwent daily cycles of 6 hours of acidic challenge at pH 4.3 followed by 17 hours of remineralization. After two weeks, fluoride varnish, APF gel, and toothpaste significantly reduced demineralization compared with the control, whereas sodium fluoride mouthwash did not demonstrate a protective effect [26].

A 2023 review by Patano *et al.* synthesized evidence on strategies to prevent white spot lesions during fixed orthodontic therapy, focusing on human clinical studies and case reports. Sixteen publications were included. The review concluded that daily acidic phosphate-based mouthwashes were more effective than weekly sodium fluoride rinses. Regular applications of ammonium fluoride varnish, CPP-ACP, and fluoride toothpaste also lowered the incidence of white spots. Additionally, CO_2 laser treatments showed promise in reducing enamel demineralization and caries risk. No notable difference was found between traditional fluoride toothpaste and formulations containing active oxygen. Overall, a combination of daily acidic phosphate mouthwashes, fluoride varnishes, CPP-ACP, and standard fluoride toothpaste appeared most effective in preventing white spot lesions, with laser therapy providing potential additional benefit [27].

Kau *et al.* investigated how different fluoride and remineralizing agents affected the development of white spot lesions in orthodontic patients. The study compared Clinpro 5000 (1.1% sodium fluoride), Clinpro Tooth Crème (0.21% sodium fluoride), and MI Paste Plus (containing CPP-ACPF). Each group included 40 participants who applied the assigned product twice daily for two minutes over a four-month period. Using the Enamel Decalcification Index (EDI) to monitor changes, the researchers found that Clinpro 5000 was most effective in reducing enamel decalcification. MI Paste Plus offered moderate protection, while Clinpro Tooth Crème showed the least efficacy, resulting in higher enamel demineralization [28].

In another 2019 study, Tahmasbi *et al.* assessed the protective effects of sodium fluoride (NaF), MI Paste Plus, and Remin Pro (a hydroxyapatite and fluoride cream) against enamel demineralization in vitro. Fourteen samples were assigned to each of four groups: a control group exposed only to pH cycling, a NaF mouthwash group, an MI Paste Plus application group, and a Remin Pro group. Treatments lasted 14 days with applications lasting five minutes following artificial saliva where applicable. Microhardness measurements revealed that NaF provided the strongest enamel protection, followed by Remin Pro and MI Paste Plus, while the control group experienced the most significant reduction in enamel hardness [29].

As part of the systematic review, the methodological quality and risk of bias were evaluated for twenty-three studies. Only two studies were classified as low risk, two as moderate risk, and the majority, nineteen studies, were identified as having high risk of bias **(Table 2)**.

Table 2. Summary of the risk of bias for RCT studies according to the Cochrane Collaboration tool

Authors and Reference	Design	Random Sequence Generation	Allocation Concealment	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Risk of Bias
Benson *et al.* [14]	RCT	Low	High	Unclear	Low	Low	High
Perrini *et al.* [16]	RCT	Low	High	Unclear	Low	Low	High
Sonesson *et al.* [17]	RCT	Low	Low	Low	Low	Unclear	Moderate
Pilli *et al.* [18]	RCT	Low	High	Low	Unclear	Low	High
Ravi *et al.* [22]	RCT	Low	Low	Low	Low	Unclear	Moderate
Rechmann *et al.* [24]	RCT	Low	Low	Low	High	Unclear	High

Sonesson *et al.* [15]	RCT	Low	Low	Low	Low	Unclear	Moderate
Kau *et al.* [28]	RCT	Low	Low	Unclear	High	High	High

The prevention of white spot lesions (WSLs) during fixed orthodontic therapy remains a prominent topic in current research, as enamel demineralization can undermine the aesthetic goals of treatment and lead to patient dissatisfaction. These lesions predominantly occur on the labial surfaces of maxillary incisors and have been reported in up to 96% of patients receiving bracket-based orthodontic care [17].

Fluoride varnishes have been repeatedly shown to mitigate WSL development during orthodontic treatment [16, 17, 18, 19, 21, 25, 28, 29]. According to Benson *et al.* [14], professionally applied "passive" fluoride interventions, such as varnishes, eliminate dependence on patient adherence by delivering fluoride directly to vulnerable enamel surfaces. While many fluoride formulations initially release high concentrations of fluoride, this effect diminishes over time, necessitating multiple applications. Benson *et al.* [14] found that reapplication every six weeks during routine orthodontic appointments did not significantly reduce WSL incidence. Likewise, Perrini *et al.* [16] observed that teeth treated with fluoride varnish over a 12-month period exhibited reduced demineralization, with anterior teeth showing the most significant improvement.

Sonesson *et al.* [15] reported that fluoride varnish is particularly effective in moderating more advanced lesions, highlighting the need to prevent severe WSLs that may require aesthetic interventions such as resin infiltration or bleaching. Earlier work by Sonesson *et al.* [17] demonstrated that varnishes containing 1.5% ammonium fluoride (7700 ppm fluoride) consistently lowered WSL occurrence. Clinically relevant remineralization was observed, with many white margins recovering within three months after bracket removal, a finding supported by Patano *et al.* [26] and Yazarloo *et al.* [19]. Additionally, Reddy *et al.* [25] reported enhanced remineralization with a varnish combining calcium, fluoride, and phosphate, which was attributed to a proprietary process that functionalizes calcium and releases free phosphate, thereby improving enamel incorporation [25].

Further investigation by Babadi Oregani *et al.* [23] evaluated varnishes with varying fluoride concentrations and found that enamel acid resistance did not differ significantly between 10,000 ppm and 22,000 ppm varnishes, though both high-concentration groups demonstrated markedly improved resistance. These results suggest that increasing fluoride dosage to an optimal level enhances preventive efficacy, reinforcing the role of fluoride varnish in WSL prevention [26].

Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and its fluoride-enriched form (CPP-ACPF) have also been studied for WSL management [13, 19, 21, 24, 28, 29]. Imani *et al.* [20] highlighted that CPP-ACP stabilizes calcium and phosphate on the enamel surface, promoting remineralization, especially when combined with fluoride. Studies show that daily use of CPP-ACP with fluoridated toothpaste can significantly reduce WSLs within a month. However, results regarding its long-term efficacy have been inconsistent, with some research, including Rechmann *et al.* [24], indicating that fluoride alone remains more effective.

The combination of CPP-ACP with fluoride appears to enhance remineralization synergistically. CPP-ACPF, enriched with fluoride, has demonstrated a pronounced effect in reversing WSLs. Multiple investigations confirm that remineralizing creams containing CPP-ACP, when used alongside fluoride toothpaste, outperform placebos, with noticeable reductions in WSLs after one month [21]. Lopatiene *et al.* further support this, reporting that fluoride-based supplements combined with CPP-ACP significantly decrease enamel demineralization during orthodontic treatment, with CPP-ACPF potentially offering superior post-orthodontic remineralization compared to fluoride mouthwash alone [13].

The study by Yazarloo *et al.* [19] similarly reports that MI Paste Plus, which contains CPP-ACP combined with fluoride, produces short-term improvements in white spot lesions (WSLs) but does not maintain long-term benefits. CPP-ACP alone was not effective in significantly reducing WSLs, yet when used alongside daily fluoride toothpaste, it demonstrated measurable efficacy [19]. In contrast, Rechmann *et al.* [24] present mixed results: although CPP-ACP appeared to enhance fluoride incorporation into dental plaque and promote enamel remineralization, the overall outcomes were inconsistent. Their interventions included quarterly MI Varnish applications, daily MI Paste Plus use, and twice-daily fluoride toothbrushing. While the experimental group exhibited a slight reduction in enamel demineralization index (EDI) scores compared to the control group, the differences were not statistically significant, and no notable differences were observed in ICDAS scores between groups [24].

Supporting Rechmann *et al.*, Tahmasbi *et al.* [29] reported that MI Paste Plus only partially limited enamel demineralization, with no significant improvement over control conditions. Although some reduction in lesion formation was observed, fluoride-based treatments were more effective [29]. Similarly, Kau *et al.* [28] compared Clinpro 5000 toothpaste, Clinpro Crème, and MI Paste Plus in preventing WSLs during orthodontic treatment. MI Paste Plus showed a lower remineralization effect than Clinpro 5000 toothpaste, highlighting the superior potential of fluoride-rich formulations [28]. Collectively, these findings reinforce the importance of fluoride-based interventions in WSL prevention during fixed orthodontic therapy. Regular, controlled fluoride exposure appears critical for strengthening enamel against demineralization, while combining CPP-ACP with fluoride may offer additional benefits, warranting further long-term investigation. Patient compliance remains a key determinant of effectiveness, particularly for mouthwashes and gels.

This review also assessed the preventive and remineralizing potential of various toothpastes, including high-fluoride formulations and other specialized compositions [14, 19, 20, 25-28]. Benson *et al.* emphasized that self-applied fluoride toothpaste is only effective when used consistently, underscoring the role of patient adherence in achieving desirable outcomes [14]. Yazarloo *et al.* [19] found that brushing twice daily for two minutes with either Clinpro 5000 or Clinpro Tooth Creme effectively prevented WSLs, yielding results comparable to MI Paste Plus. These findings are in line with Kau *et al.* (2019), who reported that Clinpro 5000 resulted in the lowest EDI percentages among the tested pastes, suggesting slightly superior performance [28]. Patano *et al.* [27] also confirmed the effectiveness of these toothpastes, further noting that toothpastes containing active oxygen were equally effective as fluoride-based formulations [27]. In addition, Sonesson *et al.* [25] demonstrated that high-fluoride toothpaste reduces biofilm metabolic activity at the enamel interface, thereby limiting demineralization and supporting remineralization [25].

Sardana *et al.* [20] similarly reported that toothpastes with higher fluoride concentrations are more effective in preventing white spot lesions (WSLs) compared to lower-fluoride formulations. Consistent with these findings, Reddy *et al.* [26] observed that participants using fluoride toothpaste exhibited significantly better prevention of orthodontically induced WSLs than the control group [26]. Beyond fluoride varnishes, CPP-ACP-based products, and high-fluoride toothpastes, research has also explored the preventive potential of various mouthwashes [18, 19, 22, 26, 29].

Pilli *et al.* [18] compared a mouthwash containing acidulated phosphate fluoride (APF, 0.044% NaF) with one containing 0.02% sodium fluoride (NaF). During the first month of orthodontic treatment, both groups experienced increased enamel demineralization and initial caries, indicating that complete prevention of WSLs is not achievable in all patients. Nonetheless, daily rinsing with APF-based mouthwash was more effective in reducing WSL formation than weekly use of neutral sodium fluoride [18]. In a similar vein, Tahmasbi *et al.* [29] evaluated sodium fluoride (NaF) mouthwash against MI Paste Plus and Remin Pro, finding that NaF produced the smallest changes in enamel microhardness, demonstrating superior efficacy in preventing demineralization [29].

Conversely, Reddy *et al.* [26] reported that a sodium fluoride mouthwash yielded slightly better outcomes than the control, but the differences were not statistically significant [26]. Ravi Kiran *et al.* [22] investigated a low-dose ammonium fluoride mouthwash and found a significant reduction in WSL scores compared to standard oral hygiene practices with fluoride toothpaste, indicating a lower WSL prevalence in the experimental group [22]. Likewise, Sardana *et al.* [20] compared a fluoride mouthwash containing 250 ppm (150 ppm NaF and 100 ppm ammonium fluoride) with a placebo and reported a significant decrease in WSL formation in the fluoride group, supporting the role of self-administered fluoride rinses in prevention [20].

This review has several limitations. Access to additional databases such as ScienceDirect and Web of Science was restricted due to subscription barriers, and Medline access was hindered by proxy limitations. Moreover, the considerable heterogeneity among the included studies precluded a robust quantitative analysis. Future research should focus on WSL staging to monitor lesion progression over time and evaluate the comparative effectiveness of fluoride, phosphopeptide-amorphous calcium compounds, and other preventive strategies. Investigating novel bioactive remineralization agents, such as nanohydroxyapatite, and conducting randomized controlled trials comparing different fluoride concentrations and delivery methods could provide clearer clinical guidance. The potential of artificial intelligence to monitor oral hygiene adherence and detect early WSLs also warrants exploration as a tool for improving preventive care in orthodontics.

For future RCTs, it is crucial to ensure adequate sample sizes, implement independent allocation concealment, conduct blinded assessments at both patient and tooth levels, and utilize validated core outcome measures. Greater emphasis should also be placed on integrating WSL-prevention technologies into routine orthodontic practice.

Research on antibacterial toothpastes and other adjunctive products shows promising results and merits further investigation. Ultimately, orthodontic treatment should not only aim to correct malocclusions but also prioritize oral health, with preventive strategies against caries gaining increasing recognition and support.

Conclusion

White spot lesions (WSLs) remain a frequent and concerning complication of fixed orthodontic treatment, with the potential to compromise both aesthetic and functional outcomes. The studies included in this review emphasize the critical importance of preventing WSLs during conventional bracket-based orthodontic therapy. In this context, the role of the orthodontist, alongside the dental hygienist, is vital in educating and motivating patients—particularly adolescents, who are at a sensitive stage of dental and behavioral development. Maintaining excellent oral hygiene is fundamental in reducing WSL risk, and this should be reinforced with daily use of high-fluoride toothpastes and mouthwashes. However, these measures alone may not always be sufficient to achieve optimal results.

Since orthodontic treatment seeks to enhance both oral function and smile aesthetics, the presence of WSLs can diminish the overall success of therapy. Therefore, incorporating additional preventive strategies, such as fluoride varnishes and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) products, is recommended, as these have demonstrated efficacy in both preventing and remineralizing enamel lesions. Evidence-based interventions, including passive fluoride applications, are especially important for patients with limited compliance. A combination of personalized oral hygiene guidance and professional or self-applied remineralizing agents provides a more comprehensive approach to minimizing WSL formation.

Future research should aim to refine treatment protocols, assess the long-term effectiveness of various interventions, and identify strategies to enhance patient adherence to preventive measures. This review also highlights the limitations of current evidence, including heterogeneity in study designs, intervention protocols, and short-term follow-up periods, which hinder the ability to draw definitive conclusions regarding the sustained efficacy of remineralization strategies. Standardized methodologies and long-term clinical trials are needed to better evaluate preventive outcomes. Furthermore, conflicting results among existing studies indicate that the preventive potential of different products is not yet fully established.

Effective WSL prophylaxis begins with selecting motivated patients and ensuring they maintain proper oral hygiene. Daily removal of plaque and food debris with fluoride-containing toothpaste forms the cornerstone of prevention. Additionally, fluoride can be administered through mouthwashes for home use, as well as gels, varnishes, or sealants applied professionally at regular intervals, tailored to individual patient needs.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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