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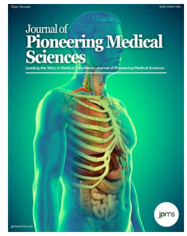

Beyond the Surface: A Deep Dive into Use of Fluoridated vs Non-fluoridated Remineralizing Agents on Permanent Teeth: A Systematic Review

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Abstract **Objectives:** Dental caries, characterized by white spot lesions (WSLs), impact approximately 49% of the population and can progress to irreversible damage if untreated. Fluoridated remineralizing agents have traditionally been the standard treatment due to their efficacy in surface remineralization. However, concerns over fluoride toxicity, including risks of dental and skeletal fluorosis, have spurred interest in non-fluoridated alternatives. This systematic review evaluates the remineralizing potential of fluoridated versus non-fluoridated agents for early enamel carious lesions in permanent teeth, focusing on clinical outcomes and patient safety. **Methods:** Adhering to PRISMA guidelines, randomized clinical trials were identified through comprehensive searches in databases such as Medline, Cochrane, Web of Science and Scopus. Inclusion criteria targeted interventions for WSLs in permanent teeth, assessing their effectiveness using DIAGNOdent scores. Studies involving diverse patient demographics, lesion severities and fluoride exposure risks were emphasized. **Results:** Six randomized clinical trials met the inclusion criteria. Both fluoridated and non-fluoridated agents demonstrated significant efficacy in remineralization. Fluoridated agents excelled in surface lesion repair, while non-fluoridated options, such as casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), showed superior performance in subsurface lesion remineralization, addressing fluoride-related safety concerns. However, variability in study methodologies and short-term follow-up limited comprehensive conclusions. **Conclusion:** Fluoridated agents remain effective for surface remineralization, but non-fluoridated alternatives offer promising solutions for deeper lesion repair and fluoride-free treatments. Long-term, standardized studies are needed to establish sustainable outcomes, enhance cost-effectiveness and guide patient-centric treatment protocols. These findings underscore the need for integrating remineralization strategies into preventive dentistry, balancing clinical efficacy with patient safety and preferences.

Key Words Remineralizing agents, fluoride, non-fluoridated alternatives, dental caries prevention, DIAGNOdent, clinical outcomes

INTRODUCTION

Dental caries, a highly prevalent condition globally, is often marked by the formation of white spot lesions (WSLs), which represent the earliest diagnosable clinical sign of enamel demineralization. WSLs affect up to 49% of the population, presenting as opaque, white patches on the enamel surface [1,2]. If untreated, these lesions can progress into incipient lesions and, eventually, cavitated lesions, extending deeper into the tooth and potentially resulting in tooth loss [3]. While natural remineralization processes involving biofilm, salivary calcium and phosphates can reverse early-stage lesions, the use of remineralizing agents, both fluoridated and non-fluoridated, significantly reduces the risk of these lesions advancing into irreversible conditions [4,5].

Fluoride-based treatments have long been the cornerstone of non-invasive dental care, improving enamel resistance to acid attacks and preventing the progression of early enamel carious lesions. However, concerns about fluoride toxicity, including dental and skeletal fluorosis, have prompted a reevaluation of its widespread use. Studies indicate that excessive and unsupervised fluoride exposure, particularly in children under six, increases the risk of fluoride poisoning and fluorosis [6,7]. These health concerns have driven a reduction in fluoride therapies in recent years and spurred interest in safer, effective alternatives.

In response to these concerns, several non-fluoridated remineralizing agents have been developed and introduced. Compounds such as casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), derived from calcium phosphate, have demonstrated substantial anti-caries properties and clinical validation [8,9]. Other fluoride-free materials include amorphous calcium phosphate (ACP), sodium calcium-phosphosilicate (bioactive glass), calcium carbonate carriers (CCC), nano-hydroxyapatite (N-Ha), trimetaphosphate (TMP), alpha-tricalcium phosphate (α-TP) and dicalcium phosphate dihydrate (DCPD), all of which function to enhance enamel remineralization [10].

Despite the promising potential of these alternatives, research directly comparing the effectiveness of fluoridated and non-fluoridated remineralizing agents for permanent teeth remains limited. There is a paucity of high-quality clinical studies assessing these agents' comparative performance in managing WSLs. This systematic review and meta-analysis aim to fill this gap by evaluating the remineralizing potential of fluoridated versus non-fluoridated agents for early enamel carious lesions in permanent teeth. These findings are critical in addressing growing consumer demand for fluoride-free options and shaping the future scope of dental care.

METHODS

Research Question

This systematic review addresses the research question, "Which among the fluoridated and non-fluoridated remineralizing agents has better potential in treating white spot lesions (WSLs)?" The primary objective is to compare the remineralizing potential of these agents for early enamel carious lesions in permanent teeth, offering evidence-based insights to improve preventive dentistry practices while addressing concerns related to fluoride safety and patient preferences.

Study Design and Inclusion Criteria

The review was conducted following PRISMA and Cochrane guidelines to ensure methodological rigor. The inclusion criteria for eligible studies are outlined in Table 1. Studies needed to focus on interventions targeting WSLs in permanent teeth, use fluoridated agents as the intervention, include non-fluoridated agents as the comparison and assess remineralization effectiveness using DIAGNOdent scores. Only randomized controlled trials (RCTs) published in peer-reviewed journals were included.

Exclusion criteria ensured the selection of clinically relevant and comparable studies. Excluded studies included those that focused on temporary or mixed dentition, addressed cavitated lesions, involved orthodontic patients (whose conditions might influence outcomes), did not directly compare fluoridated and non-fluoridated agents, or were non-randomized trials without DIAGNOdent as an outcome measure.

Table 1: Inclusion Criteria

Key Element	Criteria
Population	Permanent Dentition with White spot lesions
Intervention	Fluoridated Remineralizing Agents
Comparison	Non-Fluoridated Remineralizing Agents
Outcome	Remineralizing Potential
Study Design	Randomized Control Trials

Search Strategy

A comprehensive search was conducted across four major databases-Medline (via PubMed), Web of Science, Scopus and Cochrane-up to October 4th, 2024. To ensure robust identification of relevant studies, targeted keywords were used. Population-related terms included "permanent dentition," "adult teeth," "secondary dentition," "white spot lesions," and "subsurface remineralization." Keywords for interventions and comparisons included "fluoridated remineralizing agent," "sodium fluoride," and "fluoride gels." Outcome-related keywords included "remineralizing potential," "remineralization," "white spot reversal," and "subsurface remineralization."

Screening was conducted at both the title/abstract and full-text levels by two independent reviewers (SS and ES). Disagreements were resolved by a third reviewer (MA). To enhance comprehensiveness, reference lists of included studies were manually screened to identify additional relevant articles.

Risk of Bias Assessment

The ROB-2 tool was used to assess the quality of the included studies. This structured framework evaluates potential biases across several domains, including randomization processes, deviations from intended interventions, missing outcome data, measurement of outcomes and the selection of reported results. Each study's risk of bias was summarized in a tabular format to ensure transparency and highlight the reliability of the included evidence.

Data Collection and Limitations

Data were systematically extracted from the selected studies, focusing on sample size, intervention and control agents, outcome measures and duration of follow-up. However, several limitations were identified. Environmental factors such as patient diet, oral hygiene practices and socioeconomic diversity were not consistently reported across studies. Furthermore, many studies lacked long-term follow-ups and variability in methodologies posed challenges for direct comparisons.

Comprehensive Approach

This systematic review synthesizes findings to evaluate the comparative effectiveness of fluoridated and non-fluoridated agents for remineralizing WSLs. Fluoridated agents are well-established for surface remineralization, while non-fluoridated alternatives demonstrate potential for subsurface repair, particularly for patients with fluoride sensitivity or safety concerns. By focusing on DIAGNOdent scores as a primary outcome, this review provides reliable insights into treatment effectiveness. However, the lack of standardized reporting and limited exploration of patient-centered outcomes highlight the need for future research with more robust methodologies and diverse population samples. These findings aim to inform clinical guidelines, address patient safety concerns and contribute to developing holistic, evidence-based strategies in preventive dentistry.

RESULTS

The comprehensive search strategy was executed across four databases-Medline (via PubMed), Web of Science, Scopus and Cochrane-to identify studies relevant to the research question. This process was conducted collaboratively by two authors (SS and ES) under the supervision of a third reviewer (MA) to ensure accuracy and consistency. The initial search yielded a total of 315 articles. After the removal of duplicates, the dataset was filtered down to 168 articles (Table 2).

A thorough screening of titles and abstracts was conducted by SS and ES, reducing the pool to 17 articles deemed potentially relevant. The full text of these 17 articles was retrieved, though only 13 full texts were successfully accessed. These 13 articles were assessed in detail based on the predefined inclusion and exclusion criteria. Following this rigorous evaluation, 6 articles were finalized for inclusion in the systematic review. The selection process was reviewed and approved by MA to ensure adherence to the criteria and eliminate potential biases.

The detailed process of article identification, screening and inclusion is summarized in Figure 1.

A flow diagram illustrating the identification, screening, eligibility and inclusion of studies is referenced to provide a clear visual representation of the methodology used to select the articles. This figure aligns with PRISMA guidelines and supports transparency in the review process.

Risk of Bias Assessment

On assessing the risk of bias, 4 of the assessed articles had shown low risk of bias, whereas 2 of them showed some concerns in the assessment procedure as shown in Figure 2 and Table 3.

DISCUSSION

The comparative efficacy of fluoridated versus non-fluoridated remineralizing agents for treating white spot lesions (WSLs) in permanent teeth represents a significant area of research in modern dentistry. WSLs, which are the earliest visible signs of enamel demineralization, pose both aesthetic and structural challenges for patients. Fluoride, a long-established agent in caries prevention, enhances resistance to future carious attacks by forming acid-resistant fluoroapatite in the enamel structure [11,12]. However, concerns about fluoride overexposure, such as dental

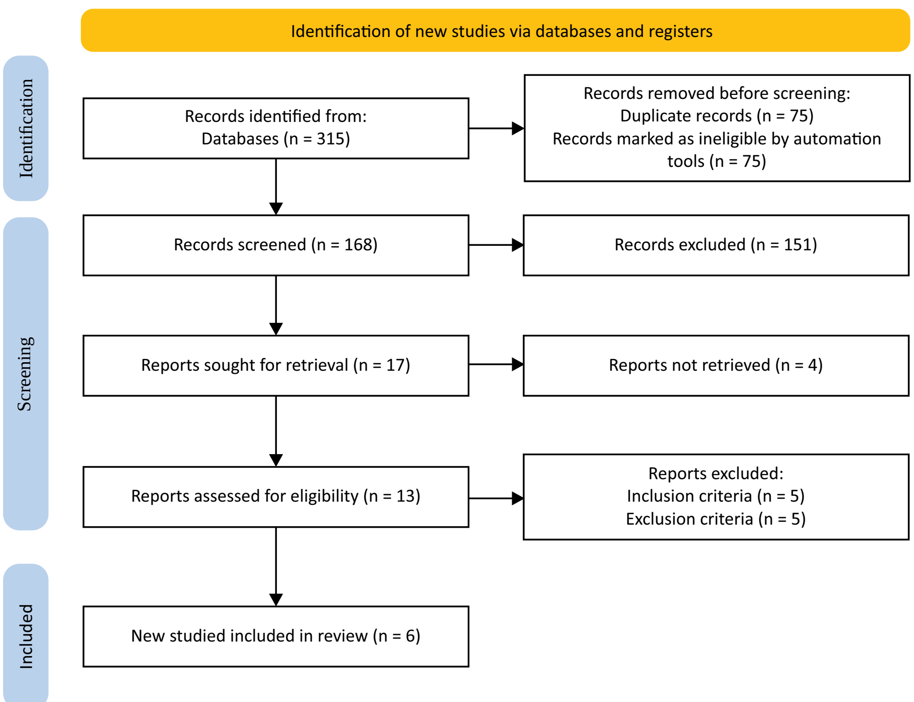

Figure 1: PRISMA Flow Diagram

Table 2: Characteristics table Data Extraction and Table

Author name	Sample Size	Intervention (G)	Control (C)	Assessment Measure	Duration	Outcome	Inference
Atteya *et al.* [16]	66	G1. Curodont Repair (P11-4), G2. Nano silver fluoride varnish (prepared at the Faculty of Pharmacy, Alexandria University)	C1. 5% NaF varnish (Duraflor®)	DIAGNOdent, NYVAD, ICDAS score	1, 3, 6 and 12 months	DIAGNOdent G1= 4, G2= 5, C=7. ICDAS G1= 20 (54.5%), G2= 21 (47.7%), C=18 (30.5%). NYVAD mean diff G1= 23, G2=8, C=11	The findings of this study highlight the remineralizing effect of P11-4 and NSF, after one year, there were no significant differences in the reduction of ICDAS scores among groups in adjusted analysis although P11-4 and NSF showed less caries activity and lower Diagnodent scores than the NaF group
Llena *et al.* [17]	786	G1. CPP-ACP (GC Tooth Mousse), G2. CCP-ACFP (Mi Paste Plus)	C1. Duraphat fluoride varnish C2. Non-Fluoridated tooth paste	DIAGNOdent, ICDAS score	1,2,3 months	DIAGNOdent G1 T0= 21.08, G2 T0=22.07, C1 T0=24.60, C2 T0=21.18, G1 T3= 13.02, G2 T3=14.72, C1 T3=16.51, C2 T3=16.33	At 1 month, G2 is superior to control, G1 is not superior to control statistically in 6-14 yr children
Gohar *et al.* [18]	58	G1. Curodont Repair	C1. Clin Pro White Varnish (3M, 3M ESPE)	DIAGNOdent, ICDAS score	3 months, 6 months	DIAGNOdent G1 T0 = 14.29, G1 T1 = 8.90, G1 T2 = 6.45. G2 T0 = 16.46, G2 T1 = 12.19, G2 T2 = 10.51 ICDAS	G1 proved to be better in successfully achieving sub-surface mineralization
Giray *et al.* [19]	23	G1. Icon-Etch Infiltrant DMG	Clin Pro White Varnish (3M, 3M ESPE)	DIAGNOdent	6 months	DIAGNOdent G1 T0 = 12.96, G1 T1 = 5.96. G2 T0 = 10.86, G2 T1 = 8.50.	G1 reduced lesion progression in single visit and provided continuity for the follow up of 6 months. This can be considered as an alternative to fluoride varnish
Singh *et al.* [20]	45	G1. CPP-ACP (GC Tooth Mousse, Plus Crème)	C1. Floritop 5%NaF Fluoride Varnish, C2. Colgate total toothpaste	DIAGNOdent	1,3,6 months	DIAGNOdent G1 T0 = 119.7 G1 T3 = 100.64, C1 T0 = 105.54, C1 T3 = 88.85, C2 T0 = 131.43 C2 T3 = 118.71	There was no added benefit of using varnish or non-fluoridated remineralizing agents in combination with fluoridated toothpaste.
Baafif *et al.* [21]	30	G1. Icon-Etch Infiltrant DMG	C1. CCP-ACFP (Mi varnish)	DIAGNOdent	1 week, 1 month, 3 months, 6 months, 12 months	DIAGNOdent G1 T0=12.214, C1 T3= 12.250, G1 T3=9.607, C1 T3=5.893	Both agents were effective in remineralizing initial white spot lesions. However, CPP-ACFP is significantly more effective than Icon-Etch resin infiltration

Table 3: Risk of bias summary

Study	D1	D2	D3	D4	D5	Overall
Atteya *et al.* [16]	Low	Low	Low	Low	Low	Low
Llena *et al.* [17]	Low	Low	Low	Low	Low	Low
Gohar *et al.* [18]	Low	Low	Low	Low	Low	Low
Giray *et al.* [19]	Low	Low	Some Concerns	Low	Low	Some Concerns
Singh *et al.* [20]	Low	Low	Low	Low	Low	Low
Baafif *et al.* [21]	Low	Low	Low	Low	High	Some Concerns

D1: Bias arising from the randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in the measurement of the outcome, D5: Bias in the selection of the reported result

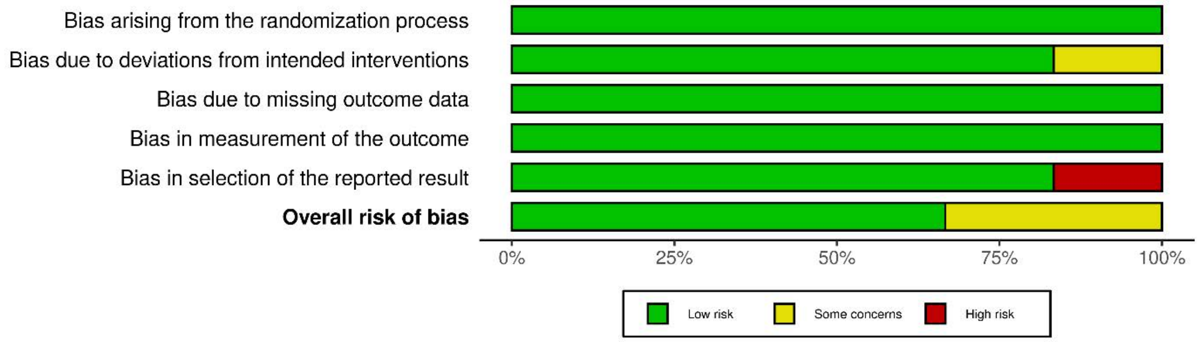

Figure 2: Risk of bias graph

fluorosis, have driven interest in non-fluoridated alternatives that offer effective remineralization without associated risks [13].

Non-fluoridated agents such as calcium phosphate-based compounds and casein phosphopeptides (e.g., CPP-ACP) have gained attention for their ability to promote mineral gain in demineralized enamel independently of fluoride [14,15]. This review synthesized existing literature to evaluate the effectiveness of these agents, focusing on their mechanisms of action, clinical outcomes and patient acceptability.

Atteya *et al.* [16] highlighted innovative non-fluoridated options like nano-silver fluoride (NSF) and self-assembling peptides (P11-4). NSF demonstrated deeper enamel penetration and superior antimicrobial and remineralizing properties compared to NaF. P11-4 facilitated hydroxyapatite regeneration through a 3D matrix, significantly reducing caries activity and lowering ICDAS scores, particularly when used alongside fluoride. However, P11-4 alone did not consistently outperform highly concentrated fluoride agents.

Llena *et al.* [17] compared fluoridated and non-fluoridated agents in subsurface lesion repair. Casein phosphopeptide-amorphous calcium fluoride phosphate (CPP-ACFP) showed greater efficacy in subsurface remineralization compared to NaF, though results for pit and fissure lesions were mixed. Both agent types demonstrated unique strengths depending on lesion location and severity, emphasizing the need for tailored treatment protocols and further long-term studies.

Gohar *et al.* [18] and Sevagaperumal *et al.* [22] noted that fluoride varnishes excel in surface-level remineralization by forming a protective calcium fluoride layer. In contrast, self-assembling peptides (SAPs) like P11-4 promote subsurface repair through scaffolding mechanisms, attracting calcium and phosphate ions from saliva. Clinical trials revealed that SAPs outperformed fluoride varnishes in subsurface lesion repair, underscoring the importance of clinical goals in agent selection.

Other studies, such as Giray *et al.* [19] and Rajendran *et al.* [25], emphasized the benefits of resin infiltration (RI), particularly for anxious patients, as it avoids invasive procedures. Resin infiltration showed superior results over fluoride varnishes in WSL treatment, suggesting its viability as an alternative for lesions resistant to non-invasive measures.

Singh *et al.* [20] found that fluoride toothpaste, fluoride varnish and CPP-ACP crème all effectively reduced WSL severity. However, combining fluoride toothpaste with varnish yielded significantly better results than toothpaste alone, while CPP-ACP provided effective fluoride-free remineralization, highlighting its importance for patients concerned about fluoride exposure.

Baafif *et al.* [21] and Kalaivani *et al.* [23] compared CPP-ACFP and resin infiltration, showing that while both agents improved DIAGNOdent scores, CPP-ACFP was more effective across all follow-up intervals. The findings stressed the importance of patient compliance and preferences, with CPP-ACFP appealing to those seeking fluoride-free options [26].

CONCLUSION

Both fluoridated and non-fluoridated agents effectively remineralize WSLs. Sodium fluoride (NaF) remains the gold standard for surface remineralization and caries prevention, while non-fluoridated options such as CPP-ACP and self-assembling peptides (SAPs) offer promising solutions for deeper subsurface repair. Non-fluoridated agents are particularly valuable for patients with fluoride sensitivity or those seeking alternative treatment options. Future research should prioritize long-term studies to refine treatment protocols, assess sustainability and address patient preferences.

Limitations

This review has several limitations. The scarcity of high-quality randomized control trials (RCTs) comparing fluoridated and non-fluoridated agents limits the generalizability of findings. Variations in study methodologies, intervention durations and outcome measures complicate direct comparisons. Many studies lacked long-term follow-ups, hindering the evaluation of sustained effectiveness. Additionally, potential publication bias may have skewed results toward positive findings. Environmental factors, such as patient diet, oral hygiene practices and socioeconomic diversity, were inconsistently reported, which could influence outcomes. These limitations underscore the need for robust, standardized studies with diverse populations and extended follow-up durations.

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Conflict of Interest

The authors declare no conflicts of interest related to this study. All efforts were made to ensure unbiased selection, analysis and reporting of the findings.

Ethical Considerations

The systematic review was conducted following ethical guidelines for research, ensuring the integrity and accuracy of the findings. No primary data involving human participants or animals were collected for this review, eliminating the need for formal ethical approval. Data privacy and source integrity were maintained throughout the research process.

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