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CONTEMPORARY REMINERALIZING AGENTS FOR INITIAL ENAMEL DEMINERALIZATION: COMPARATIVE EVIDENCE AND A RISK-ADAPTED CLINICAL FRAMEWORK

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Abstract

Background: Non-cavitated enamel demineralization is a potentially reversible stage of dental caries, but the choice of remineralizing agent is complicated by variability in formulations and clinical endpoints. Objective: To compare fluoride-based care with nano-hydroxyapatite, casein phosphopeptide–amorphous calcium phosphate (CPP-ACP), and bioactive glass in the management of early enamel lesions and to formulate an evidence-informed assessment framework. Materials and Methods: A structured narrative synthesis of selected peer-reviewed systematic reviews, randomized clinical trials, and clinical practice guidance published between 2018 and 2026 was undertaken. Information was grouped by biological mechanism, type of evidence, clinical indication, and outcome assessment. No original patient or laboratory observations were available. Results: Fluoride remains a well-supported reference intervention. A 2024 meta-analysis of nano-hydroxyapatite identified 14 eligible studies, predominantly in vitro (10), with only three in vivo and one in situ study; encouraging mineral and microhardness findings were tempered by limited clinical evidence. A separate 2024 review of nano-hydroxyapatite plus fluoride included five studies and similarly characterized clinical evidence as promising but limited. Other calcium-phosphate delivery systems and bioactive glasses show potential, although results vary with preparation, lesion activity, and outcome definition. Conclusion: Innovative remineralizing products should be evaluated as selected alternatives or adjuncts rather than assumed universally superior to fluoride. Well-controlled longitudinal studies are required to determine whether laboratory mineral gain translates into durable lesion arrest.

Keywords: enamel demineralization; early caries; white spot lesions; remineralization; fluoride; nano-hydroxyapatite; CPP-ACP; bioactive glass; minimally invasive dentistry.

Introduction

Dental enamel is a highly mineralized, non-vital tissue whose integrity depends on the balance between demineralization during acidogenic challenges and remineralization when

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calcium, phosphate, and other protective constituents are available in the oral environment. The earliest clinically visible changes may present as opaque white spot lesions (WSLs), particularly around orthodontic appliances, near plaque-retentive margins, or on surfaces exposed to repeated dietary sugar and low plaque-control effectiveness. At this non-cavitated stage, lesion arrest is possible, making timely risk assessment and conservative treatment central to contemporary cariology [1,2].

Fluoride supports enamel resistance and mineral recovery and has a substantial evidence base in nonrestorative management. Recent biomimetic materials, however, aim to provide mineral substrates or facilitate deposition within subsurface porosities. These include nano-hydroxyapatite (nHAp), casein phosphopeptide-stabilized amorphous calcium phosphate (CPP-ACP), and calcium- and phosphate-releasing bioactive glasses. Their proposed mechanisms differ and cannot be equated simply on the basis of favorable laboratory surface-hardness outcomes. A clinically meaningful comparison requires consideration of lesion depth, activity, surface integrity, caries risk, study design, duration of follow-up, and feasibility [2–6].

The objective of this article is to critically synthesize comparative evidence on innovative enamel remineralization agents and to propose a transparent, risk-adapted framework for selecting and evaluating nonoperative care. Particular attention is given to the distinction between biochemical remineralization, cosmetic masking, and true clinical arrest of non-cavitated caries.

Literature Review

The 2018 evidence-based American Dental Association guideline identified several nonrestorative modalities according to surface location and lesion severity, including 5% sodium-fluoride varnish, sealants, and other site-specific fluoride interventions. The guideline did not support routine preference for 10% CPP-ACP over available fluoride interventions [1]. Although it predates many newer formulations, its core contribution is methodological: therapeutic choice should be based on whether a specific lesion is active, cavitated, accessible, and amenable to long-term control rather than on claims about a single material.

An 18-month double-blind randomized trial involving 189 adults in its intention-to-treat population compared a hydroxyapatite toothpaste with a 1,450-ppm fluoride comparator. In the per-protocol population, 89.3% and 87.4% of participants, respectively, exhibited no increment in decayed, missing, or filled tooth surfaces; the study met its prespecified non-inferiority criterion [3]. The endpoint reflects caries prevention over time, not direct histological restoration of established enamel white spots; consequently, it should not be presented as proof that nHAp reverses all existing demineralization lesions.

In a 2024 systematic review and meta-analysis, Alajlan and Baysan examined 14 eligible studies of nHAp for WSLs, comprising ten in vitro, three in vivo, and one in situ investigation. The pooled findings suggested favorable effects on surface microhardness and mineral gain compared with fluoride in some analyses, yet the authors emphasized small clinical evidence, heterogeneity, potential bias, and short follow-up [4]. Another

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2024 systematic review evaluated five studies (four clinical and one in situ) of combined nHAp and fluoride and likewise described the available clinical findings as promising but limited [5]. In neither case is it valid to translate a pooled laboratory microhardness difference into an individual patient's probability of lesion arrest.

Other calcium-phosphate technologies also warrant cautious interpretation. CPP-ACP complexes are designed to maintain bioavailable calcium and phosphate near the enamel surface; fluoride-containing CPP-ACP formulations may offer additional chemical opportunities for mineral deposition. Bioactive glasses can release remineralizing ions and alter the local environment after contact with aqueous media. A 2025 systematic review of CPP-ACP clinical studies reported apparent benefit but inconsistent results across trials [6], while broader comparative reviews identified methodological differences that limit strong between-product rankings [7]. Milk-derived casein components additionally require consideration of patient allergy and product labeling.

Resin infiltration is often discussed alongside remineralizing products, but its primary action is penetration and occlusion of lesion microporosities with low-viscosity resin rather than direct mineral replacement. A 2026 systematic review of outcomes across 29 studies found substantial heterogeneity and inconsistent durability of several measured esthetic and clinical outcomes, reinforcing the need to separate lesion masking from remineralization [8]. It may be appropriate for selected non-cavitated lesions, but its mechanism and clinical indications differ from those of mineral-delivery agents.

Materials and Methods

The article was designed as a structured narrative evidence synthesis rather than a systematic review or an original clinical trial. The evidence set was assembled from directly accessible PubMed-indexed reviews, a randomized clinical trial, and professional nonrestorative caries guidance available through November 2026. Priority was given to publications presenting transparent study designs and measurable outcomes relevant to non-cavitated enamel lesions, including mineral gain, surface microhardness, quantitative light-induced fluorescence, lesion activity or progression, color change, and patient-level caries outcomes. The evidence was reviewed qualitatively by intervention type and clinical relevance; no prospective protocol, comprehensive PRISMA search, dual screening, pooled meta-analysis, or new patient examination was conducted for the present manuscript.

To avoid false equivalence, laboratory measurements were distinguished from clinical endpoints and from recommendations derived from formal guideline appraisal. The 14-study composition and five-study total reported in separate 2024 reviews were retained as properties of their source reviews; overlapping primary studies may occur, and these totals were not added together. Results of the randomized clinical trial were reported solely for its original caries-prevention endpoint. No study-level data were reanalyzed, and no novel significance tests or estimated treatment effects were generated.

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Results

The qualitative synthesis identified fluoride-based care as the established comparator for initial non-cavitated enamel lesions and three principal innovative mineral-delivery families: nHAp, CPP-ACP–based formulations, and bioactive glass. Results varied across outcomes, with the strongest methodological support for fluoride treatments in relevant surface-specific clinical scenarios. Evidence for newer products was generally more heterogeneous, particularly when comparing in vitro subsurface mineral recovery with patient-level lesion arrest. Table 1 summarizes clinically relevant differences without assigning unsupported numerical effectiveness rankings.

Table 1. Comparative characteristics of enamel remineralizing interventions

Intervention	Mechanistic rationale	Evidence interpretation	Clinical consideration
Fluoride varnish/toothpaste	Fluoride-mediated mineral protection and repair	Guideline-supported reference intervention [1]	Select by age, surface, risk and local protocols
Nano-hydroxyapatite	Biomimetic calcium-phosphate mineral delivery	Promising; evidence mostly laboratory-based [3–5]	Assess formulation and real-world adherence
CPP-ACP / CPP-ACPF	Stabilized calcium and phosphate reservoirs; optional fluoride	Mixed clinical comparisons; heterogeneous products [6,7]	Check casein allergy and comparator
Bioactive glass	Release of calcium/phosphate and local chemical modification	Supportive experimental evidence; formulation-dependent [7]	Clinical durability and lesion-site data needed
Resin infiltration	Porosity occlusion and optical masking	Different mechanism; variable long-term outcomes [8]	Not equivalent to mineral replacement

Figure 1 visualizes the study-design balance explicitly reported in the 2024 nHAp systematic review, revealing that most primary studies were conducted in vitro. This does not invalidate their mechanistic relevance, but it limits the strength of claims about clinical superiority in real patients. Importantly, outcomes such as hardness recovery or short-term fluorescence changes should be reported separately from cavitation prevention, visual appearance, and patient experience.

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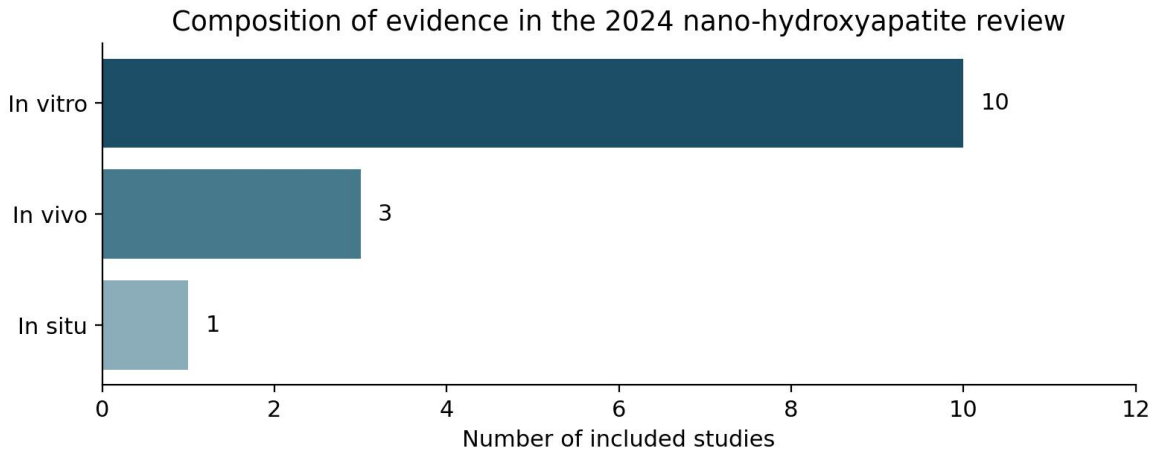


Figure 1. Study-design distribution of 14 publications included in Alajlan and Baysan (2024) [4]. Counts reproduced from the review; this is not a treatment-effect chart.

Table 2 organizes measures appropriate for future controlled investigations. Clinical lesion activity, standardized lesion photographs, and validated quantitative imaging would be integrated with adherence assessment and baseline risk. Such a design would distinguish cosmetic improvements from sustained mineral recovery and prevent attribution of changes to an adjunctive agent when fluoride exposure and home care differ between groups.

Table 2. Proposed evaluation outcomes for future clinical research

Domain	Preferred measure	Reason for inclusion
Clinical status	ICDAS lesion grade, activity, cavitation status	Directly relevant lesion-level outcome
Mineral-related change	QLF or calibrated optical measures, if validated	Quantifies longitudinal lesion behavior
Aesthetics	Standardized photographs / color difference	Separates whitening from lesion arrest
Context	Plaque index, diet, fluoride use, adherence	Controls major confounders
Safety	Tolerance, adverse events, allergy history	Patient-centered formulation assessment
Follow-up	Repeated assessments over clinically relevant intervals	Tests durability and lesion progression

The evidence-informed workflow in Figure 2 places activity and caries-risk assessment before agent selection, with reassessment afterward. It does not prescribe a universal hierarchy between nHAp, CPP-ACP, and bioactive glass; the evidence base is currently insufficient for such a ranking. For active lesions or high caries risk, patients should first receive proven site-specific nonoperative care, supported by plaque and dietary management [1].

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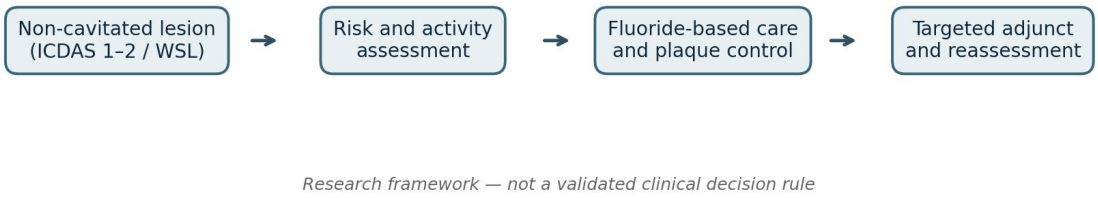


Figure 2. Proposed risk-adapted framework for early enamel lesion management; conceptual diagram, not a validated clinical algorithm.

Discussion

The growing availability of remineralizing pastes, gels, varnishes, and bioactive materials has increased therapeutic choice while complicating evidence-based comparison. Materials with convincing chemical mechanisms may yield different clinical results because mineral availability, saliva, biofilm pH, lesion permeability, application time, and patient compliance vary greatly. Consequently, the term "innovative" should describe a formulation approach, not constitute a claim of superiority. The available literature supports optimism regarding several technologies but does not justify replacing well-supported fluoride-based care across all lesion types [1,4,5].

The main methodological challenge is endpoint heterogeneity. Surface microhardness may improve while deep lesion characteristics remain unchanged; optical opacity can decrease without demonstrating long-term caries arrest, and a non-inferiority result for DMFS incidence is not interchangeable with treatment of existing white spot lesions. The comparative discussion must therefore preserve the original outcome definitions and follow-up duration. The 2023 randomized trial provides patient-level preventive evidence for hydroxyapatite toothpaste, whereas the 2024 nHAp meta-analysis largely reflects controlled laboratory models [3,4]. These findings are complementary but cannot be pooled informally into an efficacy percentage.

Another limitation involves material variability. Particle size, crystal morphology, active-agent concentration, fluoride inclusion, delivery vehicle, contact time, and accompanying oral hygiene all influence observed outcomes. CPP-ACP products may differ in concentration and in whether fluoride is included; bioactive glass formulations vary in chemical composition and ionic-release kinetics. Pooling such products into broad categories can obscure clinically significant distinctions. Further, most clinically observed WSLs arise under multiple concurrent risk factors, making direct attribution to a single remineralizing component difficult [5–7].

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Future clinical studies should be prospective, adequately powered, randomized where feasible, and ideally assessor-blinded. Prespecified primary outcomes could include the proportion of active non-cavitated lesions arrested without cavitation at 6–12 months, with secondary endpoints for mineral-sensitive imaging, appearance, satisfaction, cost, and adverse events. Studies should document baseline caries risk, patient age, lesion surface and depth, plaque control, sugar frequency, background fluoride exposure, and treatment adherence. Independent evaluation of formulation-specific effects and longer follow-up would strengthen clinical transferability.

This work has limitations intrinsic to its narrative design. The selected references do not constitute an exhaustive systematic search; publication selection was not independently duplicated and a quantitative meta-analysis was not performed. Some included reviews may share original studies, and the evidence classes cannot be compared by simple study-count totals. In addition, the present author did not provide patient records or original laboratory measurements, so the article cannot legitimately claim novel clinical effectiveness estimates. Its contribution is an integrated comparison of mechanisms, evidence maturity, and reporting priorities relevant to a prospective study in conservative dentistry.

Conclusion

Early enamel demineralization is a clinically important opportunity for minimally invasive intervention. Fluoride-based treatment and individual caries-risk control remain the established foundation of care. Nano-hydroxyapatite, CPP-ACP and bioactive glass demonstrate plausible remineralizing mechanisms and encouraging findings, but available clinical evidence does not support a universal assertion that any single innovative preparation is superior in all settings. Robust assessment should distinguish true lesion arrest from microhardness recovery and esthetic masking, account for product-specific formulation and patient-level risk factors, and include longitudinal follow-up. A future prospective trial combining standardized lesion classification with validated imaging and clinical outcomes is needed before a new remineralizing product can be recommended as an independent superior therapy.

Declarations

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